RTA 402

402-C-2002

A PHASE 2 TRIAL TO EVALUATE SAFETY, TOLERABILITY, AND EFFICACY OF BARDOXOLONE METHYL IN PATIENTS WITH CHRONIC KIDNEY DISEASE AT RISK OF RAPID PROGRESSION

VERSION 2.0 – 17 FEB 2021

Protocol Revision History

Version 1.0 – 18 NOV 2020

SPONSOR APPROVAL AND SIGNATURE PAGE

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INVESTIGATOR'S AGREEMENT

I have read the 402-C-2002 clinical study protocol, version 2.0, and agree to conduct the study as outlined. I have received and read the Investigator's Brochure for bardoxolone methyl. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Medical and Scientific Leader	[redacted]	[redacted]
Clinical Operations Personnel	[redacted]	[redacted]
Medical Monitor	[redacted]	[redacted]
SAE Reporting	[redacted]	

2. SYNOPSIS

Name of Sponsor/Company: Reata Pharmaceuticals, Inc.		
Name of Investigational Product: bardoxolone methyl		
Name of Active Ingredient: bardoxolone methyl		
Protocol Number: 402-C-2002	**Phase:** 2	**Country:** United States
Title of Study: A Phase 2 Trial to Evaluate Safety, Tolerability, and Efficacy of Bardoxolone Methyl in Patients with Chronic Kidney Disease at Risk of Rapid Progression (MERLIN)		
Study Center(s): Up to 11 study centers		
Studied Period (years): Estimated date first patient enrolled: December 2020 Estimated date last patient completed: July 2021		**Phase of Development:** 2
Population: Patients with Chronic Kidney Disease (CKD) at Risk of Rapid Progression		

Objectives:

Primary:

- To assess the change from baseline in estimated glomerular filtration rate (eGFR) at Week 12
- To assess the safety and tolerability of bardoxolone methyl

Secondary:

- To characterize the eGFR response at Week 12 across different etiologies of Chronic Kidney Disease

Exploratory:

- To characterize change in eGFR during the off-treatment period
- [redacted]

Methodology:

This multi-center, randomized double-blind, placebo-controlled, Phase 2 trial will study the safety, tolerability, and efficacy of bardoxolone methyl in qualified patients with CKD due to multiple etiologies at risk of rapid disease progression. Approximately 70 patients will be enrolled and randomized 1:1 to either bardoxolone methyl or placebo. Randomization will be stratified using the Kidney Disease: Improving Global Outcomes (KDIGO) CKD progression risk heat map (stratum 1 = yellow or orange; stratum 2 = red or dark red) based on screening eGFR and UACR using Randomization and Trial Supply Management (RTSM).

Target patient population: males and females with CKD secondary to varying etiologies will be enrolled from age 18-75 years with eGFR $\geq$ 20 to < 60 mL/min/1.73 m^2, and other risk factors for rapid progression of kidney disease. Patients with glomerulonephritis requiring immunosuppressive treatment within 6 months or a history of rapidly progressive glomerulonephritis will be excluded. No single CKD etiology (hypertensive, diabetic, or other) may enroll approximately $\geq$ 40% in the trial.

Trial design includes screening, treatment period, and off-treatment period (OT).

Screening period includes 2 visits (Screen A and Screen B), and the duration of screening (from Screen A to Day 1) may not exceed 4 weeks. The Screen A and B visits may be completed on consecutive days.

Treatment period (Day 1 through Week 12): Includes 13 visits (clinic and phone visits). Patients who successfully meet the enrollment criteria will be randomized using RTSM. Post randomization study drug will be dispensed accordingly. Day 1 of the treatment period is the day of randomization.

The maximum bardoxolone methyl dose will be determined by baseline proteinuria status. Patients with baseline urine albumin to creatinine ratio (UACR) $\leq$ 300 mg/g will be titrated to a maximum dose of 20 mg, and patients with baseline UACR > 300 mg/g will be titrated to a maximum dose of 30 mg.

Qualified patients will be randomized 1:1 to receive either bardoxolone methyl or placebo once daily (preferably in the morning) throughout a 12-week dosing period. Randomization will be stratified using the KDIGO CKD progression risk heat map (stratum 1 = yellow or orange; stratum 2 = red or dark red) based on screening eGFR and UACR using RTSM. Patients randomized to bardoxolone methyl will start with once-daily dosing at 5 mg and will dose-escalate to 10 mg at Week 2, to 20 mg at Week 4, and then to 30 mg at Week 6 (only if baseline UACR > 300 mg/g) unless contraindicated clinically, which should be discussed with the medical monitor. Patients randomized to placebo will remain on placebo throughout the study and will follow the same titration to maintain the blind. Dose de-escalation is permitted during the study if indicated clinically, and subsequent dose re-escalation is also permitted to meet the dosing objective of the highest tolerated dose.

Patients in the study will follow the same visit and assessment schedule. Patients will be assessed during treatment at Day 1, Weeks 1, 2, 4, 6, 8, and 12, and by telephone contact on Days 3, 10, 21, 31, 35, and 45. Date of last dose and the end-of-treatment assessments mark the end of the treatment period. Patients will not receive study drug during a 5-week off-treatment period between Weeks 12 and 17.

Off-treatment period (OT): Includes 5 visits requiring various assessments to characterize eGFR from the time of study drug discontinuation through Day 35 off-treatment. Patients will be assessed on Day 3 OT, Day 7 OT, Day 14 OT, Day 21 OT, Day 28 OT, and Day 35 OT. The OT day corresponds to days after last dose. Day 1 OT is the first day after receiving the last dose. Any patient who permanently discontinues study treatment early will follow the same OT assessment schedule.

End-of-study (EOS): All patients, including patients who discontinue treatment early, should complete the EOS visit 17 weeks after randomization.

All efforts should be made to follow all randomized patients for the full OT period of the trial, and the end-of-study visit (Week 17), including patients who discontinue drug early.

Number of Patients (Planned):

Approximately 70 patients will be enrolled.

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria:

1. Male and female patients 18 ≤ age ≤ 75 upon study consent;
2. Diagnosis of CKD with screening eGFR (average of Screen A and Screen B eGFR values) ≥ 20 to < 60 mL/min/1.73 m^2
   a. The two eGFR values collected at Screen A and Screen B visits used to determine eligibility must have a percent difference ≤ 25%;
3. Patient must meet at least one of the following criteria:
   a. UACR ≥ 300 mg/g; OR
   b. eGFR decline at a rate of ≥ 4 mL/min/1.73 m^2 in prior year; OR
   c. Hematuria (glomerular) defined as > 5-10 red blood cells (RBCs) per high power field (HPF, manual method), or documented history of positive urinary dipstick for blood in prior year, or macroscopic hematuria in prior 3 years;
4. Systolic blood pressure ≤ 150 mmHg and diastolic blood pressure ≤ 90 mmHg at Screen A or Screen B visit after a period of rest (≥ 5 minutes);
5. Treatment with an angiotensin-converting enzyme inhibitor (ACEi) and/or an angiotensin II receptor blocker (ARB) at the maximally tolerated labeled daily dose for at least 6 weeks prior to the Screen A visit and with no anticipated changes to dose(s) during study participation. If treatment with ACEi and/or ARB is contraindicated or not indicated, the patient must not have been exposed to an ACEi and/or ARB for at least 8 weeks prior to the Screen A visit;
6. Absolute neutrophil count > 1.5 x 10^9/L, platelets > 100 x 10^9/L, hemoglobin (Hgb) ≥ 8.0 g/dL;
7. Total bilirubin (TBL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 1.5X the upper limit of normal (ULN) both at Screen A and Screen B visits;
8. Able to swallow capsules;
9. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures;
10. Evidence of a personally signed and dated informed consent document indicating the patient has been informed of all pertinent aspects and risk of the study prior to initiation of any protocol-mandated procedures.

Exclusion criteria:

1. Prior exposure to bardoxolone methyl;
2. CKD secondary to or associated with any of the following:
   a. History of rapidly progressive glomerulonephritis (RPGN)
   b. Glomerulonephritis requiring immunosuppression in the last 6 months prior to Screen A;

3. Concomitant use of tolvaptan. Patients previously treated with tolvaptan must have discontinued drug for at least 3 months prior to Screen A visit;
4. Patients treated with polycystic kidney disease-modifying agents (somatostatin analogues) within 3 months prior to the Screen A visit;
5. Systemic immunosuppression for more than 2 weeks, cumulatively, within the 12 weeks prior to Day 1 or anticipated need for immunosuppression during the study;
6. Patients currently taking a sodium/glucose cotransporter-2 inhibitor (SGLT2i), requiring dose adjustments within 12 weeks prior to Day 1 or if dose is anticipated to change during study participation;
7. B-type natriuretic peptide (BNP) level > 200 pg/mL at Screen A visit;
8. Uncontrolled diabetes (HbA1c > 11.0%) at Screen A visit;
9. Serum albumin < 3 g/dL at Screen A visit;
10. Kidney or any other solid organ transplant recipient or a planned transplant during the study;
11. Acute dialysis or acute kidney injury within 12 weeks prior to Screen A visit or during Screening;
12. History of clinically significant cardiac disease, including but not limited to any of the following:
    a. Clinically significant congenital or acquired valvular disease
    b. Left ventricular ejection fraction < 40% (based on historical echocardiogram)
    c. History of hospitalization for heart failure within 12 months prior to Screen A
    d. New York Heart Association Class III or IV congestive heart failure (CHF)
    e. Symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or unstable angina) within 12 months prior to Screen A
    f. Pericardial constriction (based on historical echocardiogram)
    g. Restrictive or congestive cardiomyopathy (based on historical echocardiogram)
    h. Uncontrolled atrial fibrillation
    i. History of unstable arrhythmias;
13. Systolic blood pressure < 90 mmHg at Screen A visit after a period of rest;
14. Body mass index < 18.5 kg/m^2 at the Screen A visit;
15. History of malignancy within 5 years prior to Screen A visit, with the exception of localized skin or cervical carcinomas;
16. Coronavirus disease 2019 (COVID-19) diagnosis within 3 months prior to Screen A or have ever required COVID-19 related hospitalization;

17. Participation in other interventional clinical studies within 3 months (or if relevant 5 half-lives of that study medication, whichever is the longer) prior to Screen B;
18. Unwilling to practice acceptable methods of birth control (both males who have partners of childbearing potential and females of childbearing potential) during Screening, while taking study drug, and for at least 30 days after the last dose of study drug is ingested;
19. Women who are pregnant or breastfeeding;
20. Need for ongoing use of strong and/or moderate CYP3A4 inhibitors and inducers;
21. Known hypersensitivity to any component of the study drug;
22. Patient is, in the opinion of the investigator, unable to comply with the requirements of the study protocol or is unsuitable for the study for any reason.

Investigational Product, Dosage and Mode of Administration:

Bardoxolone methyl at 5, 10, 20 or 30 mg will be administered orally once daily through Week 12.

Duration of Treatment:

Bardoxolone methyl will be administered once daily through Week 12.

Reference Therapy, Dosage and Mode of Administration:

Matching placebo will be administered orally once daily through Week 12.

Criteria for Evaluation:

Efficacy endpoints:

Primary efficacy endpoint: eGFR change from baseline at Week 12.

Secondary efficacy endpoint: eGFR change from baseline at Week 12 by CKD etiology.

Exploratory efficacy endpoint: eGFR change from baseline at off-treatment Days 3, 7, 14, 21, 28, and 35.

Safety endpoints:

Laboratory results (clinical chemistry, hematology, urinalysis, and microscopy), vital sign measurements, electrocardiogram (ECG) results, weight, adverse events (AEs), and serious adverse events (SAEs).

Other endpoints:

Common genetic variants overall and by CKD etiology.

Statistical Methods:

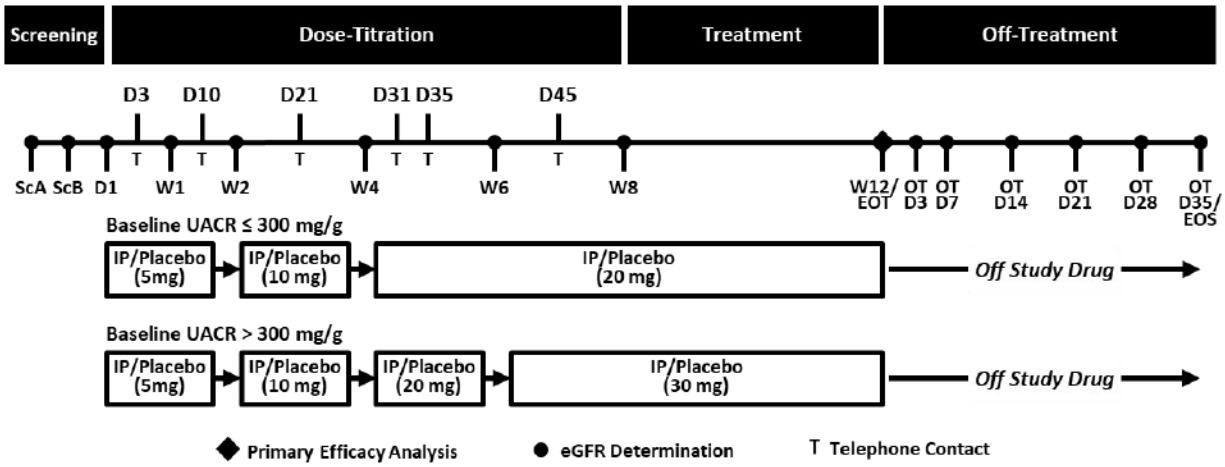
Sample size:

With 70 patients enrolled (35 in each group), the study will have approximately 80% power to detect a difference between the two treatment groups in change from baseline in eGFR of 5.9 mL/min/1.73 m^2 for the primary endpoint at Week 12. The power calculation, which was based on a two-sided two-sample t-test, assumes the following:

- Two-sided Type I error rate of 0.05;
- Standard deviation of change from baseline in eGFR of 8 mL/min/1.73 m^2;
- A change from baseline in eGFR of approximately 5.9 mL/min/1.73 m^2;
- 15% drop-out and missing data will not be imputed.

Analysis of the primary endpoint will be based on the intent-to-treat (ITT) population and analyzed using mixed-model repeated measures (MMRM) with an unstructured covariance structure. The analysis method is expected to have at least as much power as the two-sample t-test used for study planning. Appropriate sensitivity analyses of the primary analysis will be specified in the Statistical Analysis Plan (SAP). The secondary efficacy endpoint will be tested for sufficiently large subgroups, but the study is not powered to show efficacy in the secondary efficacy endpoint.

Schema for Study of Bardoxolone Methyl in Patients with CKD at Risk of Rapid Progression



Sc = Screening, UACR = urine albumin to creatinine ratio, eGFR = estimated glomerular filtration rate, EOT = end of treatment, EOS = end of study, OT = off-treatment period.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ACEi	Angiotensin converting enzyme inhibitor
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARB	Angiotensin II receptor blocker
AST	Aspartate aminotransferase
BMI	Body mass index
BNP	B-type natriuretic peptide
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations (US)
CHF	Congestive heart failure
CK	Creatine kinase
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Coronavirus disease 2019
CrCl	Creatinine clearance
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOS	End of study
EOT	End of treatment
ESKD	End stage kidney disease
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
HbA1c	Hemoglobin A1c

Abbreviation or Specialist Term	Explanation
HDPE	High-density polyethylene
Hgb	Hemoglobin
HPF	High power field
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-treat
KDIGO	Kidney Disease: Improving Global Outcomes
Keap1	Kelch-like ECH associated protein-1
Kf	Ultrafiltration coefficient
LDH	Lactate dehydrogenase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
MTLDD	Maximally tolerated labeled daily dose
Nrf2	Nuclear factor (erythroid-derived 2)-related factor 2
NT-ProBNP	N-Terminal Pro-Brain Natriuretic Peptide
OT	Off-treatment
PBO	Placebo
PH	Pulmonary hypertension
PK	Pharmacokinetic
PT	Prothrombin Time
QTc	Corrected QT interval
RBC	Red blood cell
RPGN	Rapidly progressive glomerulonephritis
RTSM	Randomization and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical analysis plan
SGLT2i	Sodium/glucose cotransporter-2 inhibitor

Abbreviation or Specialist Term	Explanation
SNGFR	Single nephron glomerular filtration rate
T2D	Type 2 diabetes
TBL	Total bilirubin
UACR	Urine albumin to creatinine ratio
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WOCBP	Women of childbearing potential

5. INTRODUCTION

Bardoxolone methyl is a semi-synthetic triterpenoid that selectively and reversibly binds to Kelch-like ECH-associated protein 1 (Keap1), resulting in potent activation of the transcription factor nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2). Through activation of Nrf2, bardoxolone methyl modulates the transcription of hundreds of genes involved in inflammation, oxidative stress, and cellular energy metabolism (Kobayashi, 2016; Wardyn, 2015).

Data from multiple animal models of chronic kidney disease (CKD) demonstrate that bardoxolone methyl and closely related structural analogs suppress inflammation and fibrosis, reduce glomerulosclerosis, prevent tubulointerstitial damage, and improve kidney function (Aminzadeh, 2014; Nagasu, 2019; Zoja, 2010). Additional studies have demonstrated that acute treatment with bardoxolone methyl reverses endothelial dysfunction and mesangial cell contraction, increases glomerular surface area (ultrafiltration coefficient, K_f), and restores single nephron glomerular filtration rate (SNGFR) without changes in intraglomerular pressure (Ding, 2013; Kidokoro, 2019).

In multiple clinical studies, treatment with bardoxolone methyl has consistently improved kidney function as assessed by either inulin clearance, creatinine clearance, or estimated glomerular filtration rate (eGFR) (Chin, 2018; de Zeeuw, 2013; Nangaku, 2020; Pergola, 2011). The increases in eGFR with bardoxolone methyl observed within the first 12 weeks of treatment have been shown to significantly correlate with longer-term changes in eGFR (Chin, 2018). Moreover, in multiple, long-term clinical studies, the treatment effect relative to placebo has been shown to persist approximately four weeks after cessation of drug (de Zeeuw, 2013; Chin, 2018, Pergola, 2011). These results are thought to reflect the drug's anti-fibrotic effects and are consistent with beneficial effects on structural remodeling observed in animal models.

The assessment of eGFR during the off-treatment (OT) period is used to assess bardoxolone methyl's effect on the irreversible loss of kidney function as well as any disease modifying effects. Available clinical pharmacodynamic and pharmacokinetic data with bardoxolone methyl suggest that acute effects on eGFR are expected to resolve within 10 to 14 days after stopping treatment. In the present study, eGFR will be assessed at multiple intervals during the OT period to characterize the timecourse of the washout of bardoxolone methyl's acute pharmacodynamic effects.

Patients with CKD with rapid progression or at risk of rapid progression are defined as those with a sustained decline in eGFR of more than 4 to 5 mL/min/1.73 m^2 per year (KDIGO, 2013). The collective clinical and nonclinical data suggest that bardoxolone methyl may be effective at ameliorating the rate of decline in eGFR in this patient population. Furthermore, increases in eGFR observed after 12 weeks of treatment may translate to a sustained eGFR response. In patients with CKD at risk of rapid progression, the potential impact of a sustained eGFR increase with bardoxolone methyl treatment may be clinically meaningful and could translate to a delay in progression to end stage kidney disease (ESKD).

5.1. Clinical Experience with Bardoxolone Methyl

Overall, bardoxolone methyl has been tested in multiple CKD studies and over 3000 individuals have been exposed to bardoxolone methyl.

5.1.1. Efficacy

As seen in Table 3, improvements in kidney function, including eGFR, creatinine clearance, and inulin clearance, have been observed with bardoxolone methyl treatment in multiple clinical studies, including those in CKD, cancer, and pulmonary hypertension (PH) patients. Bardoxolone methyl was originally considered for development in cancer patients, and in two Phase 1 studies, bardoxolone methyl was observed to reduce serum creatinine levels, corresponding to an increase in eGFR. The reductions of serum creatinine levels and resultant increases in eGFR were time-dependent and manifested in a majority (82%) of the patients studied. In subsequent studies that enrolled over 2600 patients with type 2 diabetes and CKD, bardoxolone methyl has been shown to consistently produce clinically and statistically significant improvements in eGFR that are durable for at least one year in treated patients.

Study 402-C-0804 (BEAM) was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, multi-dose, Phase 2b study designed to assess the efficacy and safety of 3 doses (25, 75, and 150 mg) of the crystalline formulation of bardoxolone methyl in patients with Stage 3b-4 CKD (eGFR 20-45 mL/min/1.73 m^2) and type 2 diabetes (T2D). Analysis of the primary endpoint, the change in eGFR values from baseline at Week 24, demonstrated a clinically and statistically significant increase in eGFR relative both to the baseline value and to the change with placebo ($p < 0.001$) at each of the 3 tested dose levels (Pergola, 2011). Mean eGFR increases were largely sustained through Week 52 and on average, patients treated with bardoxolone methyl experienced a net increase in eGFR of 7.4 ± 0.8 mL/min/1.73 m^2 at Week 52 from a baseline of 32.4 mL/min/1.73 m^2.

Study 402-C-0903, titled "Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes: The Occurrence of Renal Events" (BEACON), was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multinational, multicenter study designed to compare the efficacy and safety of bardoxolone methyl to placebo in patients with Stage 4 CKD (eGFR 15 to 29 mL/min/1.73 m^2) and T2D. A total of 2185 patients were randomized 1:1 to once-daily administration of the amorphous spray-dried dispersion formulation of bardoxolone methyl (20 mg) or placebo. The primary efficacy endpoint of the study was the time-to-first event in the composite endpoint defined as ESKD (need for chronic dialysis, renal transplantation, or renal death) or cardiovascular death. Similar to prior studies, bardoxolone methyl patients had mean increases in eGFR that occurred by Week 4 of treatment and remained above baseline through Week 48 (overall mean increase of 5.5 mL/min/1.73 m^2). In contrast, placebo-treated patients experienced a mean decline in eGFR (–0.9 mL/min/1.73 m^2, 95% CI –1.2 to –0.5 mL/min/1.73 m^2), corresponding to a relative difference between groups of 6.4 mL/min/1.73 m^2 (95% CI 5.9 to 6.9 mL/min/1.73 m^2, $p<0.001$) (de Zeeuw, 2013).

Patients in Studies 402-C-0804 and 402-C-0903 also participated in a four-week withdrawal period following the treatment period. In 402-C-0804, analysis of the change in eGFR from baseline to Week 56 for patients who received study drug for 52 weeks showed that a portion of the increase in eGFR is retained following withdrawal of therapy. Patients treated with 75 and 150 mg of bardoxolone methyl for 52 weeks had eGFR increases from baseline of 4.0 and 4.3 mL/min/1.73 m^2, respectively, at Week 56. Similar results were observed in BEACON for patients that received at least 48 weeks of treatment. These data support that the longer-term protective and anti-inflammatory effects of bardoxolone methyl may reverse some of the

structural remodeling processes in the kidney associated with declining kidney function, resulting in sustained eGFR improvement after withdrawal of drug.

Most recently, bardoxolone methyl has been shown to also significantly increase eGFR in patients with Alport syndrome (Study 402-C-1603) and autosomal dominant polycystic kidney disease (ADPKD; Study 402-C-1702).

Table 3: Cross-Study Comparison of Increases in eGFR, Inulin Clearance, and Creatinine Clearance with Bardoxolone Methyl Treatment

Study	Phase/ Country	Study Design	Study Population	# of Patients	Treatment Duration	Placebo-corrected ΔeGFR (mL/min/1.73 m²)[a]
CKD Studies						
402-C-0801 (Stratum 1)	2a/ US	Multicenter, Open-Label, Dose-Ranging, Randomized	Age >=18, Diabetic nephropathy	60	28 days	6.7[b] (p<0.001)
402-C-0801 (Stratum 2)	2b/ US	Multicenter, Open-Label, Dose-Ranging, Randomized	Age >=18, Diabetic nephropathy	20	56 days	7.2[b] (p<0.001) CrCl also sig. increased
402-C-0804 (BEAM)	2/ US	Multicenter, Double-Blinded, Randomized, Placebo-Controlled	Age >=18, T2D and CKD	227	52 weeks	8.6 at WK52 (p<0.001 vs PBO)
402-C-0902	2/ US	Multicenter, Open-Label, Randomized, Parallel-Group, Dose-Ranging	Age >=18, T2D and CKD	131	85 days	6.5[b] (p<0.001)
402-C-0903 (BEACON)	3/ Global	Multinational, Multicenter, Randomized, Double-Blinded, Placebo-Controlled	Age >=18, T2D and Stage 4 CKD	2185	Median: 7 months with 522 patients through Week 48	6.4 (p<0.001 vs PBO) CrCl also significantly increased
402-C-1102	1/US	Multi-Dose, Multicenter, Open-Label	Age>=18, T2D and Stage 3b and 4 CKD	24	56 days	9.0 (p<0.05)
RTA402-005 (TSUBAKI)	2/ Japan	Randomized, Double-Blinded, Placebo-Controlled	Age >=20, T2D and Stage 3 and 4 CKD	120	16 weeks	6.6 (inulin GFR) (p=0.008 vs PBO)
402-C-1603	2/US	Multicenter, Open-Label	Age 12 to 65, Alport syndrome	30	48 weeks	10.4 (p<0.001)
402-C-1603 Year 1	3/Global	Randomized, Double-Blinded, Placebo-Controlled	Age 12 to 70, Alport syndrome	157	48 weeks	9.5 (p<0.001 vs PBO)
402-C-1702	2/US	Multicenter, Open-Label	Age ≥ 18, ADPKD	31	12 weeks	9.3 (p<0.001)
402-C-1702	2/US	Multicenter, Open-Label	Age 18 to 70, IgA Nephropathy	26	12 weeks	8.0 (p<0.0001)
402-C-1702	2/US	Multicenter, Open-Label	Age 18 to 70, T1D CKD	28	12 weeks	5.5 (p=0.025)
402-C-1702	2/US	Multicenter, Open-Label	FSGS	18	12 weeks	7.8 (p=0.003)
Non-CKD Studies						
402-C-0501	1/ US	Open-label, Dose-Escalation	Age >=18, Advanced Solid Tumors or Lymphoid Malignancies	47	Median: 56 days	18.2[b] (p<0.0001)
402-C-0702	1/2/ US	Double-Blinded, Randomized	Pancreatic Cancer	34	Median: 56 days	32.2[b] (p=0.001)
402-C-1302 (LARIAT)	2/ US	Randomized, Double-Blinded, Placebo-Controlled	Age 18 to 75, PH (Baseline eGFR 82 mL/min/1.73 m²)	54[c]	16 weeks	14.7 (p<0.001 vs PBO)

[a] Unless noted, data are differences between mean eGFR changes from baseline for bardoxolone methyl versus placebo groups and p-values calculated comparing the difference in means between bardoxolone methyl and placebo groups. (FOOTNOTES CONTINUED NEXT PAGE)

[b] Data are mean eGFR changes from baseline for bardoxolone methyl patients and p-values are calculated from two- sided paired t-tests comparing eGFR change to 0.

[c] Number of patients enrolled in Cohorts 1 and 2.

eGFR=estimated glomerular filtration rate, CrCl=creatinine clearance, T1D=type 1 diabetes, T2D=type 2 diabetes, CKD=chronic kidney disease, PBO=placebo, ADPKD=autosomal dominant polycystic kidney disease, IgA=immunoglobulin A, FSGS=focal segmental glomerulosclerosis, PH=pulmonary hypertension.

5.1.2. Safety and Tolerability

Please refer to the Investigator's Brochure for a detailed discussion of safety findings for studies in healthy subjects, cancer, CKD, and PH patients with bardoxolone methyl.

5.1.2.1. Fluid Overload

Similar to endothelin receptor antagonists in certain patient populations, including bosentan in advanced congestive heart failure and avosentan in advanced CKD, bardoxolone methyl treatment was found to be associated with an increased risk for fluid overload and heart failure hospitalizations in the BEACON trial, which enrolled patients with Stage 4 CKD (eGFR 15 to 29 mL/min/1.73 m^2) and T2D. The overall increased risk for fluid overload and heart failure events with bardoxolone methyl appeared to be limited to up to four weeks after initiation of treatment. Elevated B-type natriuretic peptide (BNP) and prior hospitalization for heart failure were identified as risk factors that contributed to increased risk for these events. The increased risk for these events from bardoxolone methyl treatment had not been observed in six previous CKD studies, which were conducted mostly in patients with Stage 3b CKD (eGFR of 30 to 44 mL/min/1.73 m^2), patients with hepatic dysfunction, cancer patients, or healthy volunteers.

Review of admission notes and narrative descriptions for heart failure hospitalizations in BEACON indicates that heart failure in bardoxolone methyl-treated patients was often preceded by rapid fluid weight gain (several kilograms within the first weeks of treatment initiation) and was not associated with acute renal decompensation or acutely reduced left ventricular contractility. Available data from BEACON and other studies suggest that bardoxolone methyl treatment can differentially affect hemodynamic status according to the clinical condition of patients and likely promotes fluid retention in patients with more advanced renal dysfunction and other recognized risk factors associated with heart failure at baseline.

Risk mitigation procedures have been employed in subsequent trials to reduce the potential for bardoxolone methyl-induced fluid overload; these procedures excluded patients with the identified risk factors and ensured close monitoring for fluid retention within the first month of treatment.

5.1.2.2. Aminotransferase and Gamma-glutamyl Transferase Elevations

In clinical studies of bardoxolone methyl, almost all patients had increases of aminotransferase enzymes above baseline upon initiation of treatment, which followed a consistent pattern. These increases were not associated with elevations in bilirubin or other signs of liver toxicity. In BEACON, fewer hepatobiliary serious adverse events (SAEs) were observed in the bardoxolone methyl arm than in the placebo arm. The elevations begin immediately after initiation of treatment or an increase in dose; they peak approximately two to four weeks later. In most patients, aminotransferase elevations were mild, but approximately 4% to 11% of patients experienced an elevation greater than 3X the upper limit of normal (ULN). The elevations resolved to levels less than the ULN in most all patients with elevations, within two weeks after peak values while patients continued taking study drug.

Patients who experienced elevations to greater than 3X the ULN sometimes required additional time to resolve. While some patients have had elevations to above 3X the ULN, persistent

elevations to above 3X the ULN have not been observed, and the elevations did not recur once resolved, unless caused by other factors.

Bardoxolone methyl regulates gamma-glutamyl transferase (GGT), a known Nrf2 target gene protein. In clinical studies, low level GGT elevations during treatment were common, mild, and typically lasted longer than alanine/aspartate aminotransferase (ALT/AST) elevations. Bilirubin levels in patients experiencing aminotransferase or GGT elevations due to treatment with bardoxolone methyl either remained at baseline levels or decreased. The ALT, AST, and GGT elevations were generally self-limiting in patients who continued treatment with study drug.

5.1.2.3. Muscle Spasms

Muscle spasm was the most frequently reported adverse event (AE) in clinical trials of bardoxolone methyl in patients with CKD. The muscle spasms most often manifested in the first two months of treatment and resolved spontaneously or with empirical treatment. They occurred mostly at night, in the lower extremities, and were generally mild to moderate in severity. Muscle spasms may result from improved insulin sensitivity and glucose uptake in skeletal muscle cells. Increases in glucose uptake, as assessed by the hyperinsulinemic-euglycemic clamp procedure, were observed in response to bardoxolone methyl in a defined subset of patients enrolled in a Phase 2a study. To date, in those cases where serum creatinine kinase (CK) levels have been measured, no association has been observed between muscle spasms and elevated CK levels in patients treated with bardoxolone methyl. Clinical signs and laboratory findings associated with the reports of muscle spasms have not been consistent with muscle toxicity. Bardoxolone methyl subjects showed no increase in prominent laboratory findings associated with muscle toxicity, such as increased levels of serum markers, including creatinine, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), uric acid, phosphorus, and potassium, which were monitored weekly during the first two months of a prior study (402-C-0804) when muscle spasms were most frequently reported.

Increases in the whole-body glucose disposal rate have been observed in mice treated with bardoxolone methyl, as well. Increased glucose uptake was observed in isolated calf muscles of the mice, but not in white adipose tissue (Saha, 2010).

5.1.2.4. Weight Loss

Decreases in weight and reports of anorexia/decreased appetite have been observed following treatment with bardoxolone methyl in patients with CKD. In studies of these patients, 17% of bardoxolone methyl patients reported AEs of weight decrease or decreased appetite (irrespective of relationship to treatment). Weight reduction was more pronounced in patients treated with bardoxolone methyl than in those given placebo.

Weight loss of approximately one kilogram per month was observed, with patients of higher body-mass index at baseline losing more weight (in absolute terms) than those of normal or moderately-elevated body-mass index (Chertow, 2018).

5.1.2.5. Hypomagnesemia

Hypomagnesemia was reported as an AE for 15.5% of patients with T2D CKD who received bardoxolone methyl. The AE of hypomagnesemia (of any reported relationship to study drug) was more frequently reported in bardoxolone methyl-treated patients than in patients given

placebo. The investigators considered almost all reported events to be mild. Additionally, patients treated with bardoxolone methyl had a greater decrease from baseline in serum magnesium levels than patients given placebo; the decrease was evident within 4 weeks and attenuated after 8 weeks of starting therapy. In bardoxolone methyl clinical studies performed to date, a post-hoc analysis identified no correlation between hypomagnesemia and either gastrointestinal AEs or cardiac AEs, including cardiac dysrhythmias and prolonged corrected QT interval (QTc). The 24-hour urine collections from the BEACON ambulatory blood pressure monitoring sub-study showed no increase in urinary magnesium levels, indicating that renal loss of magnesium did not account for the reductions in serum magnesium observed with bardoxolone methyl treatment in CKD patients. Notably, a thorough QT study that tested doses of bardoxolone methyl up to 80 mg, bardoxolone methyl showed no increase in the QT interval (Chin, 2019).

5.1.2.6. Increases in Urinary Protein

Increases in urinary albumin have been observed in some patients treated with bardoxolone methyl with chronic kidney disease. The increases are likely due to bardoxolone methyl's pharmacological modulation of tubular protein reabsorption and have not been associated with interstitial fibrosis or injury. In preclinical studies, bardoxolone methyl has been shown to downregulate the primary proteins involved in protein reabsorption in the proximal tubules: the megalin-cubilin complex (Reisman, 2012). Moreover, the magnitude of observed eGFR increases with bardoxolone methyl treatment is thought to reduce the residence time of protein in the proximal tubules, thereby reducing protein reuptake and increasing urinary protein levels.

Therefore, increased eGFR, together with decreased megalin expression, is thought to result in decreased fractional absorption of albumin and increased urinary excretion of albumin.

Consistent with bardoxolone methyl-mediated protection in preclinical models of protein-overload-induced nephropathy, these pharmacological effects are thought to reduce protein overload and secondary nephropathy caused by excessive albumin uptake and therefore are not associated with tissue injury and interstitial fibrosis (Rossing, 2019).

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Study Objectives

The study objectives are as follows:

6.1.1. Primary Objectives

- To assess the change from baseline in estimated glomerular filtration rate (eGFR) at Week 12.
- To assess the safety and tolerability of bardoxolone methyl.

6.1.2. Secondary Objective

- To characterize the eGFR response at Week 12 across different etiologies of Chronic Kidney Disease (CKD).

6.1.3. Exploratory Objectives

- To characterize change in eGFR during the off-treatment period.
- [redacted]

6.2. Study Endpoints

6.2.1. Primary Efficacy Endpoint

- eGFR change from baseline at Week 12.

6.2.2. Secondary Efficacy Endpoint

- eGFR change from baseline at Week 12 by CKD etiology.

6.2.3. Exploratory Efficacy Endpoint

- eGFR change from baseline at off-treatment Days 3, 7, 14, 21, 28, and 35.

6.2.4. Safety Endpoints

- Laboratory results (clinical chemistry, hematology, urinalysis, and microscopy), vital sign measurements, electrocardiogram (ECG) results, weight, adverse events (AEs), and serious adverse events (SAEs).

6.2.5. Other Endpoint

- [redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This multi-center, randomized, double-blind, placebo-controlled, Phase 2 trial will study the safety, tolerability, and efficacy of bardoxolone methyl in qualified patients with CKD due to multiple etiologies at risk of rapid disease progression. Approximately 70 patients will be enrolled and randomized 1:1 to either bardoxolone methyl or placebo. Randomization will be stratified using the Kidney Disease: Improving Global Outcomes (KDIGO) CKD progression risk heat map (stratum 1 = yellow or orange; stratum 2 = red or dark red) (Section 19, Levin, 2014) based on screening eGFR and UACR using Randomization and Trial Supply Management (RTSM).

Patients with CKD secondary to varying etiologies will be enrolled from age 18-75 years with eGFR $\geq$ 20 to < 60 mL/min/1.73 m^2, and other risk factors for rapid progression of kidney disease. Patients with glomerulonephritis requiring immunosuppressive treatment within 6 months or a history of rapidly progressive glomerulonephritis will be excluded. No single CKD etiology ((hypertensive, diabetic, or other) may enroll approximately $\geq$ 40% in the trial.

The maximum target dose will be determined by baseline proteinuria status. Patients with baseline urine albumin to creatinine ratio (UACR) $\leq$ 300 mg/g will be titrated to a maximum dose of 20 mg, and patients with baseline UACR > 300 mg/g will be titrated to a maximum dose of 30 mg. Qualified patients will be randomized 1:1 to receive either bardoxolone methyl or placebo once daily (preferably in the morning) throughout a 12-week dosing period. 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 baseline UACR > 300 mg/g), unless contraindicated clinically, which should be discussed with the medical monitor (Figure 1). Dose de-escalation is permitted during the study if indicated clinically, and subsequent dose re-escalation is also permitted to meet the dosing objective of the highest tolerated dose.

Patients in the study will follow the same visit and assessment schedule. Patients will be assessed during treatment at Day 1, Weeks 1, 2, 4, 6, 8, and 12 and by telephone contact on Days 3, 10, 21, 31, 35, and 45. Date of last dose and the end-of-treatment assessments mark the end of the treatment period. Patients will not receive study drug during a 5-week off-treatment period between Weeks 12 and 17 (Figure 1).

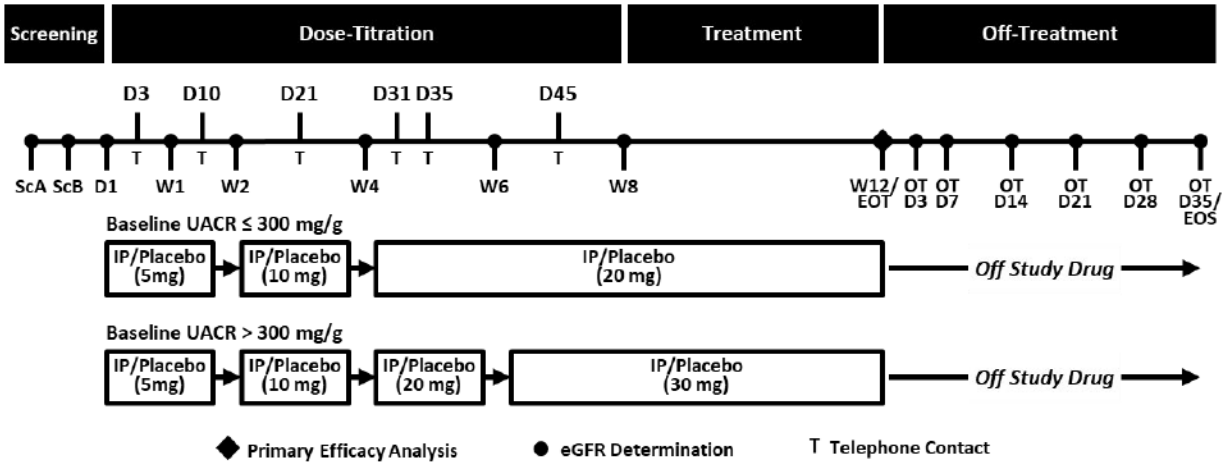
The off-treatment (OT) period includes 5 visits requiring various assessments to characterize eGFR from the time of study drug discontinuation through Day 35 off-treatment. Patients will be assessed on Day 3 OT, Day 7 OT, Day 14 OT, Day 21 OT, Day 28 OT, and Day 35 OT. The OT day corresponds to days after last dose. Day 1 OT is the first day after receiving the last dose. Any patient who permanently discontinues study treatment early will follow the same OT assessment schedule.

All patients, including patients who discontinue treatment early, should complete the end-of-study (EOS) visit 17 weeks after randomization.

All efforts should be made to follow all randomized patients for the full OT period of the trial, and the EOS visit (Week 17), including patients who discontinue drug early.

Final analysis of the primary efficacy endpoint will occur after all enrolled patients have completed their Week 17 visit (or have terminated from the trial).

Figure 1: Schema for Study 402-C-2002



Sc=Screening, UACR=urine albumin to creatinine ratio, eGFR=estimated glomerular filtration rate, EOT=end of treatment, EOS=end of study, OT=off-treatment period.

7.2. Number of Patients

Approximately 70 patients will be enrolled.

7.3. Treatment Assignment and Rationale

Qualified patients will be randomized 1:1 to receive either bardoxolone methyl or placebo once daily throughout a 12-week dosing period. Randomization will be stratified using the KDIGO CKD progression risk heat map (stratum 1 = yellow or orange; stratum 2 = red or dark red) based on screening eGFR and UACR using RTSM.

A dose-titration regimen is being utilized to allow for individual dose optimization based on tolerability and based on the anticipated maximally efficacious dose of bardoxolone methyl, which may vary based on a patient's proteinuria status at baseline. Based on results from prior trials in patients with T2D and CKD, Reata has concluded that higher bardoxolone methyl doses may be required to have an optimal effect on eGFR following drug withdrawal in patients with macroalbuminuria. Specifically, eGFR improvements in patients with normo- or micro-albuminuria were observed with a 20 mg bardoxolone methyl dose. In patients with macroalbuminuria, a 30-mg dose was required to produce a response that was similar to the patients with microalbuminuria treated at 20 mg. Consequently, the study includes dose titration up to a maximum dose of 20 mg for patients with UACR ≤ 300 mg/g and a maximum dose of 30 mg for patients with UACR > 300 mg/g, as described in Section 7.4.1. From a safety perspective, the 30 mg dose may be associated with an increased incidence of nausea; however, the nausea experienced in previous trials is generally mild, transient, and clinically manageable.

7.4. Dose Adjustment Criteria

7.4.1. Dose Escalation

Patients will receive either bardoxolone methyl or placebo once daily (preferably in the morning) throughout the study. Patients randomized to bardoxolone methyl will start with once-daily dosing at 5 mg and will dose-escalate to 10 mg at Week 2, to 20 mg at Week 4, and then to 30 mg (only if baseline UACR > 300 mg/g) at Week 6 unless contraindicated clinically, which should be discussed with the medical monitor. Patients randomized to placebo will remain on placebo throughout the study and will follow the same titration to maintain the blind. Dose escalation may need to proceed more slowly if the patient experiences early elevations in ALT/AST over ULN, e.g. at Week 2 (see Section 9.1.2). The dosing objective is to titrate patients to the maximum target dose determined by baseline UACR and maintain the maximum dose after initial dose-titration.

7.4.2. Dose De-Escalation and Re-Escalation

The investigator may choose to decrease the patient's dose to the prior dose (e.g., 20 mg to 10 mg, or 10 mg to 5 mg), if clinically indicated. Dose de-escalation may occur more than once, but the minimum dose permitted is 5 mg. Reasons for dose de-escalation should be discussed with the medical monitor and must be documented.

Once a patient's dose has been reduced, dose re-escalation back to a higher dose is permitted to meet the dosing objective. However, patients who dose re-escalate must have a telephone call 1 week after dose escalation and an unscheduled office visit 2 weeks (± 3 days) after dose escalation to collect clinical chemistry, BNP, and N-terminal proBNP (NT-proBNP). Unscheduled visits due to dose escalation should also include assessments detailed in Section 9.7.

7.5. Criteria for Study Termination

Although the Sponsor intends to complete the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons, or if required by regulatory agencies. If the Sponsor discontinues the study, all study drug will be discontinued, and the investigator will be responsible for securing any alternative therapy to be administered, as appropriate.

7.6. Schedule of Assessments

Table 4 lists the overall schedule of assessments for the study.

Table 4: Schedule of Assessments

Assessments	Screening		Treatment Period												EOT	Off-Treatment Period (Based on Date of Last Dose)					EOS[a]
	Screen A[b]	Screen B[b]	Day 1[c]	Day 3 Day 3 ±2	Wk 1 Day 7 ±3	Day 10 Day 10 ±2	Wk 2 Day 14 ±3	Wk 3 Day 21 ±2	Wk 4 Day 28 ±3	Day 31 Day 31 ±2	Wk 5 Day 35 ±2	Wk 6 Day 42 ±3	Day 45 Day 45 ±2	Wk 8 Day 56 ±3	Wk 12[a] Day 84 –3	OT Day 3 +1	OT Day 7 ±2	OT Day 14 ±3	OT Day 21 ±3	OT Day 28 ±3	OT Day 35 –3 Week 17
Visit Method	Clinic	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	Phone	Clinic	Phone	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic
Informed consent	X																				
Inclusion/ exclusion	X		X[d]																		
Demographics and baseline disease characteristics	X																				
Medical history	X																				
Collect CKD etiology	X																				
Height	X																				
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE collection			X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight in clinic	X		X		X		X		X			X		X	X						X
Weight at home[f]			X	X	X	X	X	X	X	X	X	X	X	X	X						
Dispense weight and IP diary			X				X		X			X		X							
Collect/review weight and IP diary				X	X	X	X	X	X	X	X	X	X	X	X						
ECG	X														X						X
Vital sign measurements	X[g]		X		X		X		X			X		X	X						X
Physical exam	X																				X
Targeted physical exam[h]			X		X		X		X			X		X	X						
Pregnancy test for WOCBP[i]	X	X	X		X		X		X			X		X	X						X
Study drug administration			X																		
Dispense study drug			X				X		X			X		X							
Collect/review study drug							X		X			X		X	X						
[redacted]			X																		
Clinical chemistry (incl. eGFR)	X	X	X		X		X		X			X		X	X	X	X	X	X	X	X
BNP and NT-proBNP	X		X		X		X		X			X		X	X						X
Hemoglobin A1c	X														X						
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 UACR[k]		X							X					X	X						X
PK samples[l]															X	X	X	X	X	X	X
Liver and Kidney Injury Biomarkers			X									X			X						X
C-Reactive Protein			X									X			X						X
PT/INR			X									X			X						X

[a] If a patient permanently discontinues study drug early, the patient should return as soon as possible to complete EOT procedures (i.e., those outlined at the Week 12 visit). The OT visits should then be scheduled based on the date of the last dose of study drug. Following completion of the OT visits, the EOS visit will occur at Week 17. In this case, there will be both an OT Day 35 visit scheduled 35 days following the last dose of IP and an EOS visit scheduled approximately 17 weeks after Day 1/randomization.

[b] Total Screening period should not exceed 4 weeks.

[c] Day 1 is administration of the first dose. **On Day 1, all procedures must be performed before study drug administration.**

[d] Screening eligibility procedures do not need to be repeated on Day 1; however, a review of any changes in eligibility criteria should be evaluated prior to Day 1 procedures, and a urine pregnancy test should be performed for WOCBP.

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

[f] Weights should be taken at the same time each day and recorded in a patient diary. During the first eight weeks, weights will be recorded daily; weekly weights will be recorded from Week 8 through Week 12.

[g] Blood pressure for inclusion criteria eligibility can be taken at Screen A or Screen B. Blood pressure should not be collected at Screen B if Screen A values met eligibility criteria.

[h] Investigator should evaluate if a targeted physical exam is needed, based on any symptomatology reported to the study team.

[i] 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.

[redacted]

[k] Urine albumin to creatinine ratio will be measured by first morning void spot urine collection. Containers for the collection will be provided to the patient at the visit prior to the collection.

[l] Patients must not take study drug on the day of the Week 12 visit since PK will be drawn.

7.6.1. Screening Period (Screen A & Screen B Visits)

No screening procedures may be completed prior to obtaining written informed consent. The Screening Period includes 2 visits (Screen A and Screen B), and the duration of screening (from Screen A to Day 1) may not exceed 4 weeks. The Screen A and B visits may be completed on consecutive days.

The Screen A visit must include the following assessments:

- Obtain informed consent prior to any screening procedures being performed
- Obtain demographics information (date of birth, sex, ethnicity, race)
- Record medical history, including CKD etiology and historical serum creatinine
- Perform vital sign assessments (sitting blood pressure as outlined in Section 9.10.10, pulse, heart rate, temperature, height, and weight)
- Review and record concomitant medications
- Perform 12 lead ECG (at rest)
- Perform a full physical examination
- Collect blood and urine specimens for clinical laboratory tests:
  - Serum pregnancy test (for WOCBP)
  - Clinical chemistry, including eGFR
  - BNP and NT-proBNP
  - Hemoglobin A1c
  - Hematology
  - Urinalysis and microscopy
- Assess patient eligibility
- Dispense specimen collection cup and provide instructions for collection of first morning void

The primary purpose of the Screen B visit is to obtain the 2nd baseline eGFR value.

The Screen B visit must include the following assessments:

- Review and record concomitant medications
- Perform urine pregnancy test, if applicable
- Collect blood for clinical chemistry, including eGFR
- Collect urine for UACR (first morning void brought to clinic by patient)

Blood pressure may be taken on Screen B for Inclusion criteria eligibility.

Once all screening data have been collected, eligibility for the patient should be considered, and only after confirmation the patient meets all eligibility criteria should the patient be assigned a treatment kit in the RTSM system or return for Day 1 procedures.

Patients may repeat screening once to qualify for the study (re-screening must occur at least 2 weeks after the screen fail). If a patient is approved to re-screen, they are given a new patient number and all screening procedures are completed.

7.6.2. Randomization (Day 1 Visit)

Subjects who successfully complete the screening period and are deemed eligible will return to the clinic for Day 1 procedures, including randomization. Prior to completing Day 1 procedures, continued eligibility must be confirmed. Any AEs reported prior to the first dose of study drug should be recorded in the medical history. Randomization occurs when the patient is either assigned active study drug or placebo using RTSM.

Sites should obtain at least 2 alternate points of contact for each patient randomized in the study, in an effort to avoid the patient being lost-to-follow up and the resulting missing data.

Day 1 procedures include the following:

- Assess and confirm patient eligibility
- Review and record concomitant medications
- Review and record AEs
- Perform vital sign assessments (sitting blood pressure, pulse, heart rate, temperature, and weight) as outlined in Section 9.10.10
- Dispense scale
- Dispense weight and IP diary and train patient on proper diary entry for recording daily weight and IP administration
- Perform a targeted physical examination, if needed
- Perform urine pregnancy test, if applicable
- Dispense study drug based on bottle number or kit number obtained from RTSM and instruct patient on proper administration of study drug
- Perform a buccal swab (cheek swab) for genetic testing (at any visit between Day 1 and the EOS visit)
- Collect blood and urine for clinical laboratory tests:
    - Clinical chemistry, including eGFR
    - BNP and NT-proBNP
    - Hematology
    - Urinalysis and microscopy
    - Liver and Kidney Injury Biomarkers

- C-Reactive Protein
- Prothrombin time (PT)/International normalized ratio (INR)

- Administration of the first dose of study drug **in-clinic** (record dose in the dosing diary)

7.6.3. Treatment Period (From Day 1 through Week 12)

The Treatment Period includes 13 visits (clinic and phone visits). During the Treatment Period, in clinic visits generally have a window of ±3 days, and phone visits generally have a window of ±2 days. Careful attention should be paid to visit windows beginning with the Week 12/EOT visit, which contains only a "minus" window (i.e., Week 12 should occur on Day 84−3 days). Out of window visits will result in protocol deviations.

During the Treatment Period, dose titration should be completed as outlined in Section 7.4.1.

The Treatment Period concludes at the Week 12/EOT Visit. **Patients should be instructed to refrain from taking IP on the day of the Week 12 visit. The last dose of study drug should be the day prior to the Week 12 visit.**

Labs obtained at this visit are important from an endpoint perspective, as they provide the final on-treatment eGFR values.

For detailed information on the Day 1 visit, see Section 7.6.2.

For detailed information on the Week 12 visit, see Section 7.6.4.

Treatment Period clinic visits between Day 1 and up to Week 12 (Week 1, Week 2, Week 4, Week 6, and Week 8) must include the following assessments:

- Review and record concomitant medications
- Review and record AEs
- Perform vital sign assessments (sitting blood pressure, pulse, heart rate, temperature, and weight) as outlined in Section 9.10.10
- Dispense weight and IP diary and train patient on proper diary entry for recording daily weight and IP administration (Day 1, Week 2, Week 4, Week 6, and Week 8)
- Collect/review weight and IP diary (Week 1, Week 2, Week 4, Week 6, and Week 8)
- Perform a targeted physical examination, if needed
- Perform urine pregnancy test, if applicable
- Dispense study drug based on bottle number or kit number obtained from RTSM and instruct patient on proper administration of study drug (Day 1, Week 2, Week 4, Week 6, and Week 8)
- Collect and review study drug (Week 2, Week 4, Week 6, and Week 8)
- Perform a buccal swab (cheek swab) for genetic testing (at any visit between Day 1 and the EOS visit)

- Collect blood and urine for clinical laboratory tests:
  - Clinical chemistry, including eGFR
  - BNP and NT-proBNP
  - Hematology
  - Urinalysis and microscopy
  - Urine for UACR – first morning void specimen (Week 4 and Week 8)
  - Liver and Kidney Injury Biomarkers (Week 6)
  - C-Reactive Protein (Week 6)
  - PT/INR (Week 6)
- Dispense specimen collection cup and provide instructions for collection of first morning void (Week 2, Week 6, and Week 8)

Phone Visits (Day 3, Day 10, Week 3, Day 31, Week 5, and Day 45) must include the following assessments:

- Review and record prior concomitant medications
- Review and record AEs
- Review weight and IP diary

7.6.4. Week 12 (End of Treatment) Visit

Week 12 is the final visit in the Treatment Period, and it marks the transition to the OT Period. Careful attention should be paid to ensure the visit is scheduled between Day 81 and Day 84, as outlined in Table 4.

Patients should be instructed to refrain from taking IP on the day of the Week 12 visit. The last dose of study drug should be the day prior to the Week 12 visit.

If a patient permanently discontinues study drug early, please refer to Section 8.3.

Assessments to be completed at the Week 12/EOT Visit include the following:

- Review and record concomitant medications
- Review and record AEs
- Perform vital sign assessments (sitting blood pressure, pulse, heart rate, temperature, and weight)
- Collect/review weight and IP diary
- Perform 12 lead ECG at rest
- Perform a targeted physical examination, if needed
- Perform urine pregnancy test, if applicable
- Collect and review study drug

- Perform a buccal swab (cheek swab) for genetic testing (if not already collected)
- Collect blood and urine for clinical laboratory tests:
    - Clinical chemistry, including eGFR
    - BNP and NT-proBNP
    - Hemoglobin A1c
    - Hematology
    - Urinalysis and microscopy
    - Urine for UACR - first morning void specimen
    - Liver and Kidney Injury Biomarkers
    - C-Reactive Protein
    - PT/INR
- Collect blood for PK

7.6.5. Off-Treatment Period (OT Day 3 to OT Day 35)

The OT Period includes 5 visits and includes various assessments to characterize eGFR from the time of drug discontinuation through Day 35 off-treatment. AEs and SAEs should continue to be collected during this period.

All visits in the OT Period should be scheduled based on the date of the Week 12/EOT visit.

If a patient permanently discontinues study drug early, please refer to Section 8.3.

The OT period must include the following assessments:

- Review and record prior concomitant medications
- Review and record AEs
- Collect blood for clinical chemistry, including eGFR
- Collect blood for PK

7.6.6. End of Study (EOS) Visit (OT Day 35)

The End of Study visit refers **to the last visit for a patient and must** include the following assessments**:**

- Review and record concomitant medications
- Review and record AEs
- Perform vital sign assessments (sitting blood pressure, pulse, heart rate, temperature, and weight)
- Perform 12 lead ECG (at rest)
- Perform a physical examination

- Perform a buccal swab (cheek swab) for genetic testing (if not already collected)
- Collect blood and urine specimens for clinical laboratory tests:
  - Urine pregnancy test (for WOCBP)
  - Clinical chemistry, including eGFR
  - BNP and NT-proBNP
  - Hematology
  - Urinalysis and microscopy
  - Urine for UACR
  - Liver and Kidney Injury Biomarkers
  - C-Reactive Protein
  - PT/INR
- Collect blood for PK

If a patient permanently discontinues study drug early, please refer to Section 8.3.

7.6.7. Unscheduled Visits

Unscheduled visits are defined as any visit outside of the protocol specified visits due to any of the reasons outlined in Section 9.7. At a minimum, unscheduled visits should include collection of AEs, review of concomitant medications, and measurement of vital signs. Unscheduled visits may also include other assessments such as laboratory assessments, including blood collection for PT/INR, physical exams, etc. Any procedures completed at an unscheduled visit should be fully documented in the source in the clinical database. Additional conversations may be necessary with the medical monitor following an unscheduled visit to assess patient safety.

7.7. Home Health Provider Use

Due to the COVID-19 outbreak and restrictive measures put in place by local governments and sites, the study may face challenges including travel restrictions, limited availability of site access and personnel, and limitation on the movement of individuals. To address these challenges, home health services may be implemented by the Sponsor to assist with the completion of study required visits and laboratory assessments while guaranteeing the rights, safety, and wellbeing of participants and of the trial sites' staff. The use of a company, delegated by the Sponsor, specialized in home health services ensures the ongoing safety monitoring of trial participants and trial integrity through the collection of critical data, in accordance with the Food and Drug Administration (FDA) and local guidelines about the COVID-19 pandemic management. The site will be provided with the following documentation for any home health nurse conducting procedures for patients enrolled at that site: signed and dated curriculum vitae, current Nursing Licensure, good clinical practice (GCP) training certificate, and protocol training certificate. The home health nurse/professional will also be included in the site's Delegation of Authority log.

Tasks delegated to the home health nurse/professional may include collection of vital signs and weight measurements, collection of information about AEs and concomitant medications, collection of laboratory samples (blood and urine), PK sample collection, supply urine pregnancy test for WOCBP for self-reading, drug dispensation and accountability, and diary dispense/review/collection. Laboratory samples will be collected using the central laboratory kit and will be processed and shipped according to the laboratory manual for the study. All costs relevant to these additional services will be covered by Reata Pharmaceuticals.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

Diagnosis and main criteria for inclusion:

1. Male and female patients 18 ≤ age ≤ 75 upon study consent;
2. Diagnosis of CKD with screening eGFR (average of Screen A and Screen B eGFR values) ≥ 20 to < 60 mL/min/1.73 m^2
   a. The two eGFR values collected at Screen A and Screen B visits used to determine eligibility must have a percent difference ≤ 25%;
3. Patient must meet one of the following criteria:
   a. Urine albumin to creatinine ratio (UACR) ≥ 300 mg/g; OR
   b. eGFR decline at a rate of ≥ 4 mL/min/1.73 m^2 in prior year; OR
   c. Hematuria (glomerular) defined as > 5-10 red blood cells (RBCs) per high power field (HPF, manual method), or documented history of positive urinary dipstick for blood in prior year, or macroscopic hematuria in prior 3 years;
4. Systolic blood pressure ≤ 150 mmHg and diastolic blood pressure ≤ 90 mmHg at Screen A or Screen B visit after a period of rest (≥ 5 minutes);
5. Treatment with an angiotensin-converting enzyme inhibitor (ACEi) and/or an angiotensin II receptor blocker (ARB) at the maximally tolerated labeled daily dose for at least 6 weeks prior to the Screen A visit and with no anticipated changes to dose(s) during study participation. If treatment with ACEi and/or ARB is contraindicated or not indicated, the patient must not have been exposed to an ACEi and/or ARB for at least 8 weeks prior to the Screen A visit;
6. Absolute neutrophil count > 1.5 x 10^9/L, platelets > 100 x 10^9/L, hemoglobin (Hgb) ≥8.0 g/dL;
7. Total bilirubin (TBL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 1.5X the upper limit of normal (ULN) both at Screen A and Screen B visits;
8. Able to swallow capsules;
9. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures;
10. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study prior to initiation of any protocol-mandated procedures.

8.2. Subject Exclusion Criteria

All patients with any of the following conditions or characteristics must be excluded from the study:

1. Prior exposure to bardoxolone methyl;
2. CKD secondary to or associated with any of the following:
   a. History of rapidly progressive glomerulonephritis (RPGN)
   b. Glomerulonephritis requiring immunosuppression in the 6 months prior to Screen A
3. Concomitant use of tolvaptan. Patients previously treated with tolvaptan must have discontinued drug for at least 3 months prior to Screen A visit;
4. Patients treated with polycystic kidney disease-modifying agents (somatostatin analogues) within 3 months prior to the Screen A visit;
5. Systemic immunosuppression for more than 2 weeks, cumulatively, within the 12 weeks prior to Day 1 or anticipated need for immunosuppression during the study;
6. Patients currently taking a sodium/glucose cotransporter-2 inhibitor (SGLT2i), requiring dose adjustments within 12 weeks prior to Day 1 or if dose is anticipated to change during study participation;
7. B-type natriuretic peptide (BNP) level > 200 pg/mL at Screen A visit;
8. Uncontrolled diabetes (HbA1c > 11.0%) at Screen A visit;
9. Serum albumin < 3 g/dL at Screen A visit;
10. Kidney or any other solid organ transplant recipient or a planned transplant during the study;
11. Acute dialysis or acute kidney injury within 12 weeks prior to Screen A visit or during Screening;
12. History of clinically significant cardiac disease, including but not limited to any of the following:
    a. Clinically significant congenital or acquired valvular disease
    b. Left ventricular ejection fraction < 40% (based on historical echocardiogram)
    c. History of hospitalization for heart failure within 12 months prior to Screen A
    d. New York Heart Association Class III or IV congestive heart failure (CHF)
    e. Symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or unstable angina) within 12 months prior to Screen A
    f. Pericardial constriction (based on historical echocardiogram)
    g. Restrictive or congestive cardiomyopathy (based on historical echocardiogram)
    h. Uncontrolled atrial fibrillation

i. History of unstable arrhythmias;

13. Systolic blood pressure < 90 mm Hg at Screen A visit after a period of rest;
14. Body mass index < 18.5 kg/m^2 at the Screen A visit;
15. History of malignancy within 5 years prior to Screen A visit, with the exception of localized skin or cervical carcinomas;
16. Coronavirus disease 2019 (COVID-19) diagnosis within 3 months prior to Screen A or have ever required COVID-19 related hospitalization;
17. Participation in other interventional clinical studies within 3 months (or if relevant 5 half-lives of that study medication, whichever is the longer) prior to Screen B;
18. Unwilling to practice acceptable methods of birth control (both males who have partners of childbearing potential and females of childbearing potential) during Screening, while taking study drug, and for at least 30 days after the last dose of study drug is ingested;
19. Women who are pregnant or breastfeeding;
20. Need for ongoing use of strong and/or moderate CYP3A4 inhibitors and inducers;
21. Known hypersensitivity to any component of the study drug;
22. Patient is, in the opinion of the investigator, unable to comply with the requirements of the study protocol or is unsuitable for the study for any reason.

8.3. Patient Discontinuation and Termination

Patients have the right to discontinue study drug or withdraw from study follow-up at any time for any reason, without prejudice to their medical care. Furthermore, the investigator may discontinue a patient from study drug. Consultation with the medical monitor should occur. The reason for a patient's discontinuation from study drug or study termination will be recorded in the electronic case report form (eCRF). Any patient who discontinues study drug for 14 consecutive days or more must have approval from the medical monitor prior to resuming treatment with study drug.

8.3.1. Patient Study Drug Discontinuation Criteria

Study drug discontinuation refers to a patient's stopping administration of study drug. Reasons for study drug discontinuation may include the following:

- ADVERSE EVENT [Occurrence of an AE or change in medical status that will lead the investigator to be concerned about the patient's welfare];
- DEATH;
- LOST TO FOLLOW UP [Patient lost to follow-up];
- NON-COMPLIANCE WITH STUDY DRUG [Subject has not agreed with or not adequately followed the instructions related to the study medication];
- OTHER [Other specified reason for patient discontinuation];
- PHYSICIAN DECISION [Specified medical reason for patient discontinuation];

- PREGNANCY [Females who become pregnant during the study];
- PROTOCOL-SPECIFIED WITHDRAWAL CRITERIA MET [Reached ESKD];
- PROTOCOL DEVIATION [Non-compliance with protocol]
- STUDY TERMINATED BY SPONSOR;
- SITE TERMINATED BY SPONSOR;
- WITHDRAWAL BY SUBJECT.

The temporary discontinuation and reason for discontinuation must be recorded in the eCRF.

Patients who permanently discontinue study drug *prior to the Week 12 study visit* should be brought back to the clinic as soon as possible to complete the procedures associated with the Week 12 visit (i.e., end-of-treatment visit). For patients who permanently discontinue study drug early, and *during a scheduled study visit*, the Week 12 assessments should be completed at that visit.

To minimize missing data in the OT period, all patients who permanently discontinue study drug early should be encouraged to complete all visits and assessments in the OT period, and patients should return to complete the Week 17/EOS visit as outlined in the Schedule of Assessment (see Table 4) unless, in the rare occurrence, the patient terminates participation in the study. As an example, if drug is permanently discontinued at Week 5, the patient would return as soon as possible for EOT procedures. The date of the patient's last dose would be the start of the OT period, and the patient would complete all OT visits and assessments (OT Days 3, 7, 21, 28, and 35) over the next 5 weeks. At the patient's target Week 17 date (based on date of randomization), the patient should return to the clinic to complete EOS procedures as the final data collection.

8.3.2. Patient Study Termination Criteria

Study termination refers to a patient's stopping all study follow-up, which includes study assessments, visits, and all contact with the site regarding the trial. Reasons for early study termination include the following:

- DEATH;
- LOST TO FOLLOW-UP;
- WITHDRAWAL OF CONSENT BY SUBJECT.

Every reasonable effort should be made to maintain contact with all patients enrolled in the study. If contact is lost, the PI or study personnel should attempt contact with the alternate contacts provided by the patient, the site should attempt to reach the patient through any possible method including phone, email, text, and through a certified letter. Contact must have been attempted by both the PI and the study team, prior to a patient being considered lost to follow up. Patients should not be considered lost to follow-up until the scheduled Week 17/EOS visit date.

The term "withdrawal of consent" should be used only when the patient no longer wishes to participate in the trial and no longer authorizes investigators to make efforts to continue to obtain their outcome data. Unless the patient provides their written withdrawal of consent or there is other written documentation by the investigator confirming the patient's verbal intent to

completely withdraw from the trial, patients should be followed for all protocol specified evaluations and assessments. The investigator should inquire about the reason for withdrawal of consent, request the patient return all unused investigational product, request the patient return for end-of- treatment and follow-up visits (if applicable), and follow-up with the patient regarding any unresolved AEs. Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a patient's intended withdrawal need to be completely understood, documented and managed to protect the rights of the patient and the integrity of the trial.

If a subject is discontinued early from the study, the date the subject is withdrawn from the study and the reason for withdrawal will be recorded on the eCRF.

In case of discontinuation from study, the EOT visit assessments should be performed, and any unresolved AEs or SAEs will be followed up according to Section 11.2.1.1.

Patients who discontinued drug and also choose to terminate participation in the trial should be brought back to the clinic as soon as possible for early termination assessments (i.e., Week 12 end-of-treatment visit).

9. TREATMENT OF PATIENTS

9.1. Select Management Guidelines

The guidelines below apply to the management of study participants.

9.1.1. Management of Fluid Status

Specific risk mitigations procedures will be employed to reduce the potential for bardoxolone methyl-induced fluid overload. These procedures include exclusion of patients with any severe kidney disease, defined as an eGFR value of < 20 mL/min/1.73 m^2. To exclude patients with significant cardiac dysfunction, the study will exclude patients with a history of clinically significant cardiac disease. Patients who have evidence of volume overload at baseline, defined as BNP level of > 200 pg/mL, will also be excluded.

Laboratory data and rapid weight gain will also be used to monitor fluid status after randomization. Patients who experience a BNP >100 pg/mL that represents a doubling (or more) of BNP levels from Day 1 should have an unscheduled telephone contact immediately (see Section 9.10.15 for description of telephone contact). In addition, patients will be given a Sponsor-provided scale to use at home to collect and record their weights daily during the first 8 weeks of the treatment period and weekly thereafter. Patients who experience a five-pound (2.3 kilograms) or greater increase in weight since their Day 1 weight during the first 8 weeks must have an unscheduled telephone contact immediately. Whether due to BNP elevations or weight gain, if clinically important fluid retention is suspected, the patient must be instructed to stop taking their study medication immediately and be medically evaluated by the investigator or a local physician within 1 to 2 days.

Investigators are encouraged to consider starting or increasing doses of diuretics (thiazides, loop diuretics) early after recognition of edema. This can be done concurrently with temporary drug discontinuation and re-initiation. Patients may not restart their study medication until the investigator has completed and documented an assessment of fluid overload.

Beyond Week 8, patients who experience a weight increase of five pounds (2.3 kilograms) or greater compared to Day 1 will be instructed to contact the clinic to assess the need for an unscheduled physical examination and laboratory assessment by the investigator. Study medication should not be discontinued unless clinically important fluid retention is suspected. If suspected, the patient must be instructed to stop taking their study medication immediately and be medically evaluated by the investigator or a local physician within 1 to 2 days.

Investigators should advise patients to watch for signs and symptoms of fluid overload. Patients should be informed to notify their physicians immediately if they experience swollen feet, chest pain, shortness of breath with mild exertion or while lying down, or other relevant symptoms.

The investigator must immediately assess symptoms of fluid overload and determine appropriate medical management, as necessary, including whether stopping drug administration is required.

9.1.2. Management of Elevated Aminotransferase Levels (ALT and/or AST)

Nearly all instances of elevated aminotransferases due to bardoxolone methyl treatment are expected to be asymptomatic. Some patients may experience more rapid increases in ALT/AST

values than others during the dose titration period. Investigators may consider extending the time between each dose increase from two weeks to four weeks to manage ALT/AST elevations.

Check aminotransferase levels (as well as TBL, GGT, alkaline phosphatase (ALP), and International Normalized Ratio [INR]) within 72 hours if the following occurs:

- ALT or AST levels > 3X ULN.

Repeat testing every 72 to 96 hours until aminotransferase levels are below 3X the ULN for at least one week. Patient should be followed until aminotransferase level returns to normal. Testing for patients not located near the investigator (such that it is impractical to return to the site at the required intervals) may be performed at a local lab and sent to the investigator and medical monitor for review, by approval from the medical monitor.

Discontinue study drug administration permanently if any of the following occur:

- ALT or AST > 8X ULN;
- ALT or AST > 5X ULN for more than 2 weeks;
- ALT or AST > 3X ULN and (TBL > 2X ULN **or** INR > 1.5);
- ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

The hepatobiliary tree must be visualized (e.g., ultrasound, magnetic resonance imaging [MRI]) and assessed if a patient discontinues taking study drug secondary to elevated transaminase levels. Additional tests and imaging may be warranted depending on the clinical presentation.

9.1.3. Management of Muscle Spasms

Basic symptomatic relief is the first step in managing muscle spasm, including walking, adequate hydration, wearing socks, and stretching before bedtime. Assessment of levels of electrolytes such as magnesium, calcium, and potassium may indicate the need for replacement. Serum vitamin D levels may be collected by the investigator, in the evaluation of muscle spasms. If vitamin D levels are low, supplementation may be warranted. Muscle relaxants may also help relieve symptoms.

9.1.4. Weight Loss

Ongoing assessments to ensure that the patient is receiving adequate nutrition and consideration of other etiologies of weight loss may be warranted for patients receiving bardoxolone methyl.

9.1.5. Hypomagnesemia

In instances where a patient experiences hypomagnesemia, defined as serum magnesium less than 1.3 mEq/L (0.65 mmol/L), consideration should be given to repletion of serum magnesium.

9.1.6. Management of Urinary Protein

Although increases in urinary protein with bardoxolone methyl have not been associated with kidney injury or loss of kidney function, investigators should closely monitor patients if urinary albumin to creatinine ratios increase by more than 100% and exceed 1000 mg/g for proteinuria and should consult the medical monitor for appropriate measures.

9.1.7. Management of Blood Pressure

Investigators should attempt to maintain the blood pressure within the range recommended by the Kidney Disease Blood Pressure Working Group : ≤ 140 mmHg systolic and ≤ 90 mmHg diastolic for patients with UACR < 30 mg/g, and ≤ 130 mmHg systolic and ≤ 80 mmHg diastolic for patients with UACR > 30 mg/g (KDIGO, 2012).

Patients being treated with an ACEi and/or ARB should be receiving the maximally tolerated labeled daily dose (MTLDD), defined as the dose at or below the labeled dose that does not exhibit any intolerable adverse effects (e.g., hypotension, hyperkalemia), based on the investigator's assessment. If the patient is currently receiving one drug (ACEi or ARB) below the maximum labeled dose, the drug should be titrated to the MTLDD based on the assessment of tolerability by the investigator at least 6 weeks prior to the Screen A visit.

Diuretics may be titrated to help maintain blood pressure target levels.

Any changes in ACEi or ARB use or diuretic therapy should be preceded by consideration of any relevant contraindications as per the local product information.

9.1.8. Nausea

Nausea may occur with higher doses of bardoxolone methyl. Nausea AEs are typically mild and reversible within a few weeks after treatment initiation. If symptoms do not resolve, dose de-escalation, with consultation of the medical monitor, may be reasonable.

9.1.9. End Stage Kidney Disease

Patients approaching ESKD should be closely monitored by the investigator to fully characterize their progression. For patients with eGFR ≤ 15.0 mL/min/1.73 m^2, initiate more frequent follow-up to closely monitor safety assessments (i.e., clinical chemistry (incl. eGFR), hematology, vital sign assessments (incl. weight), BNP and NT-proBNP). Similar frequent follow-up may also be implemented for patients with eGFR > 15.0 mL/min/1.73 m^2 who, in the investigator's opinion based on the anticipated progression of their disease, may be approaching ESKD. Patient follow-up should be at least once every 4 weeks (± 2 weeks), until one of the following occurs:

- Initiation of dialysis;
- Receipt of transplant.

If a patient will imminently initiate dialysis or receive a transplant, the patient should be brought in for an EOT visit in order to have EOT/Week 12 assessments conducted, if at all possible (prior to ESKD date).

Upon initiation of dialysis or receipt of kidney transplant, study drug should be permanently discontinued. Following permanent study drug discontinuation due to initiation of dialysis or receipt of kidney transplant, patients should continue to be followed only for vital status and SAEs by phone or in person according to the planned contact schedule in Section 7.6 through their scheduled Week 17 visit date. See Section 8.3 for procedures following permanent study drug discontinuation. Initiation of dialysis and receipt of kidney transplant due ESKD should be considered important medical events, and as such recorded as SAEs.

9.2. Description of Study Drug

Bardoxolone methyl (RTA 402) drug product information is shown in Table 5. Information regarding the matching placebo is shown in Table 7.

Table 5: Bardoxolone Methyl Drug Product Information

Description	**Bardoxolone methyl capsule (5 mg and 15 mg)**
Ingredients	Bardoxolone methyl Methacrylic Acid – Ethyl Acrylate Copolymer (1:1), Type A Silicified Microcrystalline Cellulose Hydroxypropyl Methylcellulose Lactose Monohydrate Sodium Lauryl Sulfate Colloidal Silicon Dioxide Magnesium Stearate Gelatin capsules Titanium Dioxide (capsule pigment)
Route of Administration	Oral

Table 6: Placebo Product Information

Description	**Placebo capsule (5 mg and 15 mg)**
Ingredients	Silicified Microcrystalline Cellulose Lactose Monohydrate Magnesium Stearate Gelatin capsules Titanium Dioxide (capsule pigment)
Route of Administration	Oral

9.3. Concomitant Medications

9.3.1. Excluded Medications

Patients taking these medications or treatments will be ineligible for enrollment:

- Tolvaptan;
- Somatostatin analogues;

- Other interventional clinical studies within 3 months (or if relevant 5 half-lives of that study medication, whichever is the longer) prior to Screen B;
- Chronic (> 2 weeks) immunosuppressive therapy, or need for corticosteroids, including therapies such as glucocorticoids, oncologic preparations, and anti-TNFα agents [e.g., infliximab (Remicade®), adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®)] within 12 weeks prior to Day 1. Glucocorticoid intra-articular injections, inhaled products, topical preparations, and nasal preparations are allowed.

Patients who take excluded medications during the study should not discontinue study drug solely on this basis. Consultation with the medical monitor should occur prior to study drug discontinuation or withdrawing a patient from the study.

Concomitant use with strong or moderate CYP3A4 inhibitors and inducers is prohibited. If a strong or moderate CYP3A4 inhibitor/inducer is medically necessary, study drug should be temporarily discontinued. Examples include but are not limited to:

- CYP3A4 Inhibitors: Itraconazole, clarithromycin, erythromycin, ritonavir, indinavir, and verapamil
- CYP3A4 Inducers: carbamazepine, phenytoin, apalutamide, bosentan, and efavirenz

9.3.2. Permitted Medications

Allowed concomitant medications include the following:

- Antibiotics;
- Daily multivitamins or recommended daily supplements;
- Other medications intended to manage concurrent diseases, as authorized by the treating physician;
- Oral, implantable, or injectable contraceptives.

Patients taking medication chronically, including ACEi, ARBs, and SGLT2i, should be on stable doses at the time of study enrollment and maintained on those same doses and dose schedules throughout the study period and should not have additions or changes made to their medications, unless medically indicated.

9.4. Treatment Compliance

The investigator or his/her designated and qualified representatives will only dispense study drug to patients enrolled in the study in accordance with the protocol. Patients should administer study drug exactly as instructed by the site. Non-compliance is defined as taking less than 80% or more than 120% of expected study medication during any evaluation period (visit to visit).

Patients should record in the patient diary all administered and missed doses of study drug. The reason for a missed dose should be recorded in the patient diary. A missed dose includes drug holidays and temporary study drug discontinuations. Patients will be asked to return all unused study drug (study drug bottles and any unused capsules).

9.5. Randomization

Qualified patients will be randomized 1:1 to bardoxolone methyl or placebo at Day 1 using RTSM. Randomization will be stratified using the KDIGO CKD progression risk heat map (stratum 1 = yellow or orange; stratum 2 = red or dark red) based on screening eGFR and UACR using RTSM.

9.6. Blinding

In this double-blind, placebo-controlled study all patients, investigators, site personnel, and laboratories with direct involvement in the conduct of the study or their designees will be blinded to treatment assignments. To prevent potential bias, appropriate measures will be taken to ensure the blind is maintained for the patients and personnel mentioned previously. To maintain the blind, investigators will distribute blinded study drug bottles and treatment kits to patients as directed by the RTSM. Investigators and patients will not be blinded to dose level, but will be blinded to treatment assignment (i.e., active study drug versus placebo).

For patient unblinding, the investigator is encouraged to contact the medical monitor to discuss situations in which he or she believes that the blind should be broken, but ultimately the investigator has the right to break the blind (e.g., in the event of a serious or life-threatening medical situation).

If unblinding is required, the investigator will utilize RTSM to perform the unblinding. If a study drug assignment is unblinded, the investigator must describe the event that required unblinding in the patient's source documents.

Patients must discontinue taking the study drug if their treatment assignment has been unblinded to the investigator (or designee). Such patients must undergo the same study discontinuation procedures as those patients who discontinue taking study drug for other reasons.

Patient treatment assignments must not be unblinded in the case of an AE or SAE except as described above.

Unblinding for Regulatory Submission:

In situations where regulation requires unblinding and reporting of a particular serious AE, the appropriate bodies (e.g., ECs, IRBs, regulatory agencies) must be provided with unblinded information according to the applicable regulatory requirement. This information must not be conveyed to any investigator, site personnel or patient; therefore, this type of unblinding does not necessitate that the patient discontinues taking study drug. In cases when unblinded information must be conveyed to local health authorities, personnel without direct involvement in the conduct of the study must be responsible for unblinding the patient's treatment utilizing RTSM and conveying the necessary information.

9.7. Unscheduled Visits

Unscheduled visits are allowed for the following reasons:

- Assessment of weight gain per Section 9.1.1;
- Management of an AE or SAE;

- Performance of additional laboratory tests for clinically abnormal laboratory test values or to confirm a possible pregnancy;
- Dose re-escalation;
- Dose de-escalation;
- eGFR ≤ 15.0 mL/min/1.73 m^2 per Section 9.1.9;
- Any time the investigator feels that it is clinically appropriate for patient safety.

At a minimum, unscheduled visits should include collection of AEs, concomitant medications, and vital signs. Additional conversations may be necessary with the medical monitor following an unscheduled visit to assess patient safety.

9.8. Pregnancy

9.8.1. Women of Childbearing Potential and Fertile Males

Women of childbearing potential (WOCBP) are those who have experienced menarche and are not surgically sterile (no history of bilateral tubal ligation, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), do not have fallopian inserts with confirmed blockage (e.g., X-ray, ultrasound), have not had reproductive potential terminated by radiation, and are not postmenopausal (defined as no menses for at least 1 year without an alternative medical cause).

Fertile males are those who have entered puberty or reached physical maturation (after puberty) and are not surgically sterile (no history of bilateral orchiectomy or vasectomy at least 6 months earlier with the appropriate post-procedure documentation of surgical success).

9.8.2. Methods of Birth Control

During Screening, while taking study drug, and until 30 days following administration of the final dose of study medication, WOCBP must practice one of the following acceptable methods of birth control:

- Use double barrier contraception method defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream, diaphragm [always use with spermicidal jelly/cream]);
- Use of hormonal contraceptives (oral, parenteral, intravaginal, or transdermal) for at least 90 days prior to start of study drug administration;
- Use of an intrauterine device;
- Vasectomized partner (with vasectomy performed at least 6 months prior to screening with the appropriate post-procedure documentation of surgical success). Partner *must* be the sole partner for that patient;
- Abstain from sexual intercourse completely. Complete abstinence from heterosexual intercourse is only acceptable if it is the preferred and usual lifestyle of the individual. Periodic abstinence is not permitted.

During Screening, while taking study drug and until 30 days after the final dose of study medication is taken, fertile males who have female partners of childbearing potential must practice one of the following methods of birth control:

- Use double barrier contraception method, defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream, diaphragm [always use with spermicidal jelly/cream]);
- Partner contraception methods; must be the sole partner for that patient:
  - Use of an intrauterine device;
  - Use of hormonal contraceptives (oral, parenteral, intravaginal or transdermal) for at least 90 days prior to start of study drug administration;
  - Surgically sterile partner (bilateral tubal ligation, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy); fallopian inserts with confirmed blockage (e.g. X-ray, ultrasound);
  - Reproductive potential has been terminated by radiation;
  - Postmenopausal (defined as no menses for at least 1 year) without an alternative medical cause;
- Abstain from sexual intercourse completely. Complete abstinence from heterosexual intercourse is only acceptable if it is the preferred and usual lifestyle of the individual. Periodic abstinence is not permitted.

9.8.3. Suspected Pregnancy

During the study, all WOCBP must be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., late or missed menstrual period). Male patients must be instructed to contact the investigator if a sexual partner suspects she may be pregnant.

If a patient or investigator suspects that the patient may be pregnant, the study drug must be withheld until the results of a serum pregnancy test are available. If the serum pregnancy test confirms the pregnancy, the patient must permanently discontinue taking study drug. The investigator must immediately report to the medical monitor a pregnancy associated with study drug exposure. The early discontinuation protocol-required procedures outlined for End-of-treatment and Follow-up visits must be performed on the patient.

Pregnancy is not considered an AE; however, the investigator must follow a pregnant patient, or the pregnant female partner of a male patient (if consenting), and report follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants resulting from such pregnancies should be followed for a minimum of 8 weeks. Reata or designee may contact the investigator to request additional information throughout the course of the pregnancy.

The following pregnancy outcomes must be considered SAEs and will require additional reporting in the eCRF and reported as a serious AE:

- Congenital anomaly/birth defect;
- Stillbirth;
- Spontaneous miscarriage.

9.9. Serious Toxicities

In the case of serious toxicities, the investigator may choose to interrupt treatment with bardoxolone methyl. Dose reductions are permitted to manage tolerability issues. Patients who resume therapy after an interruption will follow the originally planned study schedule.

9.10. Study Procedures

The following sections describe each assessment. The timing of these assessments is noted in Table 4. All Day 1 procedures, except AE assessments, should be completed prior to administration of first dose of study drug.

A Central Laboratory should be used for all lab-based assessments. For specific guidance on lab sample collection, processing, and shipment, please refer to the Laboratory Reference Manual.

9.10.1. Informed Consent

Written informed consent (see Section 15.3) must be obtained from the patient before any study-related procedures are performed, and again if there is a change in the study procedures that would affect the patient's willingness to participate. The informed consent should be reviewed in detail by the patient and the principal investigator or his/her designee. Sites must ensure all pages of the informed consent are reviewed, and initialed and dated, as appropriate, prior to commencing study procedures. The principal investigator or designee must ensure the patient fully understands the potential risks and benefits of trial participation. A copy of the signed and dated informed consent form must be provided to the patient. The original informed consent form should be filed in the patient's records and must be made available to the sponsor and/or monitor.

9.10.2. Inclusion/Exclusion

Inclusion and exclusion criteria must be reviewed as indicated in Table 4. Patients must meet all of the inclusion and none of the exclusion criteria for entry in the study. Investigators should contact the medical monitor with any questions regarding eligibility prior to the patient's enrollment in the study on Day 1.

9.10.3. Demographics and Baseline Disease Characteristics

Demographic data including sex, age, race, and ethnicity, will be collected as indicated in Table 4. Baseline disease characteristics will be collected as indicated in Table 4.

9.10.4. Prior and Current Concomitant Medications

The name, dose, and frequency must be recorded for all medications the patient is taking. All allowed and excluded medications should be recorded including all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Trade or generic drug names should be used where possible. Prior and concomitant medications (i.e., medications the patient is taking or has taken within 30 days prior to Day 1) must be reviewed as indicated in Table 4 and all changes recorded in the source documentation and clinical database.

9.10.5. Medical History

A complete medical history, covering the past 5 years prior to screening, as self-reported by the patient, must be collected. Medical history also includes collection of historical serum creatinine values for the past 5 years. There is no minimum requirement for the number of historical values collected. Sites should aim to obtain 1 to 2 values for each year, for the past 5 years prior to screening. Medical history will be recorded as indicated in Table 4.

9.10.6. CKD Etiology

CKD etiology(s) should be collected and recorded as indicated in Table 4.

9.10.7. Height

Height should be measured without footwear or prosthetics as indicated in Table 4.

9.10.8. Weight and Body Mass Index (BMI)

Weight must be measured as indicated in Table 4. BMI will be calculated in the eCRF each time the weight is recorded. The Sponsor will provide scales for distribution to patients for use at home to measure weight, and a patient diary will be provided to record the at-home weight measurements. Weights recorded in patient diaries will not be entered in the eCRF. Weights should be taken at the same time each day and recorded in a patient diary. During the first eight weeks, weights will be recorded daily; weekly weights will be recorded through Week 12. Patients will be instructed to stop administering study drug and contact the investigator if their daily weight increases during the first 8 weeks per the criteria outlined in Section 9.1.1. Patients will be provided instructions within the Informed Consent Form to help ensure consistent weight collection throughout the study.

9.10.9. Electrocardiograms (ECG)

A 12-lead ECG will be recorded as indicated in Table 4 after the patient has rested for at least 10 minutes in a supine position. The heart rate from the ECG machine should not be used as part of the vital sign measurements.

9.10.10. Vital Sign Measurements

Vital sign measurements include the patient's pulse rate (beats/minute taken for at least 15 seconds), respiration rate, and body temperature. Blood pressure should be taken after the patient has rested in a sitting position for at least 5 minutes. Take and record 3 blood pressure recordings; each recording must be 2 minutes apart. Discard the 1st reading and then average the 2nd and 3rd readings. The average of the 2nd and the 3rd readings must be used for the purpose of

the trial (e.g., inclusion/exclusion criteria). The same arm (usually the non-dominant arm) and the appropriate size cuff should be used for each measurement. Vital sign measurements should be taken as indicated in Table 4.

9.10.11. Physical Examination & Targeted Physical Examination

A comprehensive physical examination must be performed by a physician, physician assistant, or registered nurse practitioner as indicated in Table 4 and as documented within the table footnotes. The examination must include the following organ or body system assessments: head, eyes, ears, nose, throat, musculoskeletal, cardiovascular, lymphatic, respiratory, abdomen, skin, extremities, and neurological. Assessments of any specific signs or symptoms reported by the patient must also be performed and documented along with any other findings of note. Clinically significant findings at Screening must be addressed in medical history, (i.e., findings should be attributable to a diagnosis recorded in medical history). Following the examination at Screening, new or changed physical examination findings meeting the definition of an AE must be reported as an AE. If possible, the same individual should perform each physical examination on a patient during the study.

A targeted physical examination (symptom-directed) will be performed as needed at visits indicated in Table 4.

9.10.12. Pregnancy Test

WOCBP (see Section 9.8) will complete a pregnancy test as indicated in Table 4, or at any time if pregnancy is suspected. Negative test results are required on Day 1 before study drug administration. Any patient who becomes pregnant during the study must discontinue taking study drug immediately. WOCBP will require a serum pregnancy test (hCG-Qual) at the Screen A visit or at any point in time if a pregnancy is suspected.

See Section 9.8.3 for a description of procedures to be followed in case of pregnancy.

9.10.13. Study Drug Administration

Patients should self-administer the number of capsules instructed from each bottle included in the study drug bottle/kit orally once a day beginning on Day 1 through the end of the treatment, as indicated in Table 4. Each dose of study drug should be administered at approximately the same time each day, preferably in the morning. Study drug administration (IP) should be recorded in a patient diary throughout the 12-week dosing period. Patients must not self-administer study drug the day of the Week 12 Visit. The last dose of drug should occur the day prior to the Week 12 Visit.

A vomited dose must not be replaced. A double dose (e.g., missed dose from previous day and dose for current day) must not be taken.

9.10.14. Study Drug Dispensation and Collection

Study drug will be dispensed to the patient and collected from the patient as indicated in Table 4. The patient will be dispensed one bottle at Day 1 and treatment kits at Week 2, Week 4, Week 6 (only if baseline ACR > 300 mg/g) and Week 8. Only one treatment kit should be opened at a

time. Dispensed treatment kits from each visit (including unscheduled visits) should be returned to the site for collection at the subsequent visit.

9.10.15. Telephone Contact

Patients will be contacted by telephone as indicated in Table 4. Patients will be asked about their body weight and other signs of fluid retention, as well as AEs and any changes to concomitant medications. If fluid retention is suspected, the patient should be instructed to stop taking study medication immediately and be medically evaluated by the investigator or a local physician within 1 to 2 days, as detailed in Section 9.1.1.

9.10.16. Adverse Event Collection

Patients will be observed for general appearance, presence of illness or injury, or signs indicative of a concurrent illness as indicated in Table 4. Patients must be instructed to volunteer any information regarding AEs on or after the first dose of study drug or query the patients with an open question regarding any AEs they may be experiencing (e.g., "How have you been feeling since your last visit?"). Any findings are to be documented. Patients must be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (including prescription drugs, over-the-counter medications, vitamins, herbal products, and minerals). Responses must be documented in the source documents.

9.10.17. Genetic Testing

A buccal swab (cheek swab) will be collected on or before the EOS visit to be used for genetic testing as indicated in Table 4. The testing panel will assess approximately 18 genes known to be associated with chronic kidney disease.

9.10.18. Clinical Chemistry

Samples will be collected for the following clinical chemistry analyses as indicated in Table 4: ferritin, CK, BUN, enzymatic creatinine, eGFR, TBL, direct bilirubin, ALT, AST, ALP, sodium, potassium, calcium, phosphorus, uric acid, total protein, glucose, albumin, LDH, magnesium, chloride, bicarbonate, and GGT.

9.10.19. eGFR

The eGFR values collected at Screen A and Screen B visits will be averaged to determine eligibility. The two eGFR values used to determine eligibility must have a percent difference ≤ 25%, as determined by the following calculation:

Percent Difference = |X-Y| / ((X+Y)/2)

X=1st eGFR value (Screen A)

Y=2nd eGFR value (Screen B)

|X-Y|=absolute value of the difference between the two eGFR values

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation will be used:

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

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. Age indicates age at time of lab collection.

9.10.20. N-Terminal Pro-B-type Natriuretic Peptide (NT-proBNP) and B-type Natriuretic Peptide (BNP)

Samples will be collected for NT-proBNP and BNP as indicated in Table 4. As recent exercise may affect BNP and NT-proBNP levels, patients should be allowed to rest for one hour following arrival at the clinic and prior to obtaining this blood sample. This sample must be taken with the patient in the same position at all appropriate visits, e.g., sitting or semi-recumbent.

Detailed instructions on collection, storage and shipment of the sample will be provided in a separate laboratory manual provided to the investigator.

9.10.21. Hemoglobin A1c (HbA1c)

Samples will be collected for HbA1c as indicated in Table 4. Detailed instructions on collection, storage, and shipment of the samples will be provided in a separate laboratory manual provided to the investigator.

9.10.22. Hematology

Samples will be collected for the following hematology assessments as indicated in Table 4: hematocrit, hemoglobin, 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).

9.10.23. Urinalysis and Microscopy

Samples will be collected for the following urinalysis and microscopy assessments as indicated in Table 4: specific gravity, ketones, pH, protein, blood, glucose, clarity, color, leukocytes, nitrite, bilirubin, and a microscopic examination (if indicated based on laboratory results).

9.10.24. Urine Collection for Urine Albumin to Creatinine Ratio (UACR)

Urine albumin to creatinine ratio will be measured by first morning void spot urine collection as indicated in Table 4. Appropriate containers for the collection will be provided to the patient at the visit prior to the collection.

Patients should be instructed how to properly capture a sample of their first morning void, defined as their first urination after 5 AM. Following Day 1, if a patient presents for a visit and has forgotten to collect (or bring) the urine sample(s) for that visit, they may return within 7 days to submit the sample(s) collected that day.

9.10.25. Pharmacokinetic (PK) Blood Samples

Blood samples for determination of plasma bardoxolone methyl and potential metabolite concentrations will be drawn as indicated in Table 4. Patients must be instructed to not take their study drug prior to coming to the clinic for the Week 12 visit. Patients will be asked by site personnel to provide the time of their last two administrations of study drug prior to the blood sample being collected at Week 12. **Patients should be instructed to refrain from taking IP on the day of the Week 12 visit. The last dose of study drug should be the day prior to the Week 12 visit.** Blood sample collection instructions should be referenced in the laboratory manual.

The date and time of collection of all PK blood samples should be recorded. Dates in the case report form should be recorded in an unambiguous format (e.g., DD MMM YYYY) and time should be recorded to the nearest minute (e.g., HH:MM using the 24-hour clock). Blood samples not drawn should be recorded as such.

9.10.26. Liver and Kidney Injury Biomarkers

Blood samples for novel liver and kidney injury biomarkers will be drawn as indicated in Table 4. On Day 1, blood sample must be collected before study drug administration.

9.10.27. C-Reactive Protein

Blood samples will be drawn as a marker of inflammation as indicated in Table 4. On Day 1, blood sample must be collected before study drug administration.

9.10.28. Prothrombin Time (PT) / International Normalized Ratio (INR)

Blood samples will be drawn to help monitor the clotting of the blood as indicated in Table 4.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

Bardoxolone methyl and placebo capsules, 5 mg (size #4) and 15 mg (size #1) will be used in this study. Kits will be provided for the 10 mg, 20 mg, and 30 mg doses using a combination of 5 mg and/or 15 mg capsules.

10.2. Study Drug Packaging and Labeling

The study drug will be supplied as either individual bottles (5 mg dose) or in tamper-evident kits containing two high-density polyethylene bottles (10 mg, 20 mg, and 30 mg doses) or the matching placebo capsules. Each bottle will utilize foil induction-seal liners and a child-resistant closure. Each bottle of study drug will contain 30 capsules of bardoxolone methyl or matching placebo. Each bottle will also contain a desiccant insert that must not be ingested. Labeling on each kit bottle will contain at minimum the following information:

- Medication ID number;
- Bardoxolone methyl capsules (strength) or matching placebo
- Protocol 402-C-2002;
- Caution Statement: New Drug – Limited by Federal Law to Investigational Use.
- Keep out of reach of children;
- Control or lot number;
- Store at 15° – 25°C (59° – 77°F);
- Reata Pharmaceuticals, Inc., Plano, TX 75024.

When applicable, a double-panel label will be presented on the treatment kit carton containing this and other information as well. Additionally, labeling, in the relevant local languages for investigational medicinal product for use and distribution in the European Union shall adhere to current Eudralex, Volume 4 Annex 13 guidance and requirements.

10.3. Study Drug Storage

Investigative sites must store the investigational product in a secure location with room temperature conditions of 15° - 25°C (59° - 77°F).

10.4. Study Drug Administration

Please refer to Section 9.10.13 for details on study drug administration. Clear instructions will be provided to the patient regarding the number and type of capsules to be ingested at each study drug administration time point listed in Table 4. Patients must be instructed to continue taking study drug once daily throughout a 12-week dosing period: (1) the patient has been otherwise instructed by the investigator or (2) the patient has been formally discontinued from study treatment. **Patients should be instructed to refrain from taking IP on the day of the Week 12 visit. The last dose of study drug should be the day prior to the Week 12 visit.**

10.5. Study Drug Accountability

The investigator, or designee, will maintain a record of all study drug received, dispensed, and returned to the Sponsors' designee. No study drug shall be destroyed by the clinical site unless directed in writing to do so by the Sponsor's quality assurance department. Study drug bottles and any unused capsules should be returned to the study staff for eventual disposition by the Sponsor. The number of capsules returned at each visit will be recorded by the site for each bottle in the kit.

10.6. Study Drug Handling and Disposal

At the conclusion of the study or in an instance of planned study drug replacement, the Sponsor or its designee will direct the site regarding the final disposition of study drug.

10.7. Compliance

The prescribed dosage, timing, and mode of administration of study drug may not be changed. Patients will be asked questions regarding compliance and any departures from the intended regimen must be recorded in the eCRF. Patients will be asked to return all unused study drug. Non-compliance is defined as taking less than 80% or more than 120% of study drug during any evaluation period (visit to visit).

11. SAFETY ASSESSMENTS

11.1. Safety Parameters

To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all safety assessments. Safety parameters include vital sign measurements, ECG results, AEs, SAEs, weight, and laboratory test results (clinical chemistry, hematology, urinalysis, and microscopy).

11.2. Adverse and Serious Adverse Events

11.2.1. Definition of Adverse Events

11.2.1.1. Adverse Event

An AE is defined as any untoward medical occurrence in a patient regardless of its causal relationship to study drug. An AE can be any unfavorable and unintended sign (including any clinically significant abnormal laboratory test result), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study-drug related. Included in this definition are any newly occurring events or previous condition that has increased in severity or frequency since the administration of study drug.

All AEs that are observed or reported by the patient during the study (from time of administration of the first dose at the Day 1 visit until the final visit indicated in Table 4) must be reported, regardless of their relationship to study drug or their clinical significance.

11.2.1.2. Serious Adverse Event

As SAE is any AE occurring at any dose and regardless of causality that:

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

The term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Important medical events are those that may not meet any of the criteria defined above; however, they may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the SAE definition.

Pregnancy is not considered an AE; however, information will be collected for any pregnancies that occur during the study (from the time of the first dose of study drug until the final visit indicated in Table 4, as appropriate). Certain pregnancy outcomes will require submission as an SAE (see Section 9.8).

The investigator is responsible for reporting to Reata or designee all AEs and SAEs that are observed or reported by the patient during the study (from the time of administration of the first dose of study drug until the final visit indicated in Table 4, as appropriate), including events resulting from protocol-associated procedures as defined in relevant legislation, and regardless of their relationship to study drug or their clinical significance. The Sponsor may request additional information from the investigator to ensure the timely completion of accurate safety reports.

All SAEs reported or observed during the study must be followed to resolution or until the investigator deems the event to be chronic or the patient to be stable. Reata or designee may contact the investigator to obtain additional information on any SAE which has not resolved at the time the patient completes the study.

11.3. Eliciting Adverse Event Information

At every study visit, patients must be asked a standard, non-directed question, such as, "How have you been feeling since your last visit?" to elicit any medically related changes in their well-being. They may also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (including prescription drugs, over-the-counter medications, vitamins, herbal products, and minerals). Responses must be documented in the source documents.

In addition to patient observations, AEs must be documented for any clinically significant diagnosis resulting from abnormal laboratory test values, physical examination findings, or ECG abnormalities, or from other documents that are relevant to patient safety.

11.4. Assessment of Causality

The investigator must use the following classifications and criteria to characterize the relationship or association of the study drug in causing or contributing to the AE:

Not Related: This relationship suggests that there is no association between the study drug and the reported event.

Unlikely Related: This relationship suggests that the temporal sequence of the event with study drug administration makes a causal relationship improbable and/or other factors also provide plausible explanations.

Possibly Related: This relationship suggests that treatment with the study drug caused or contributed to the AE. That is, the event follows a reasonable temporal sequence from the time of study drug administration, and/or, follows a known response pattern to the study drug, but could have been produced by other factors.

Probably Related: This relationship suggests that a reasonable temporal sequence of the event with study drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment

based on the investigator's clinical experience, the association of the event with study drug administration seems likely.

Definitely Related: This relationship suggests that a definite causal relationship exists between the drug administration and the AE, and other conditions (e.g., concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

11.5. Assessment of Severity

The investigator will grade the severity of the AEs as mild, moderate, or severe using the following definitions:

Mild: Symptoms causing no or minimal interference with usual social and functional activities, intervention not indicated.

Moderate: Symptoms causing greater than minimal interference with usual social and functional activities, local or noninvasive intervention indicated.

Severe: Symptoms causing inability to perform usual social and functional activities, medical/surgical intervention indicated.

11.6. Recording Adverse Events

All conditions present prior to the administration of the first dose of study drug (Day 1) should be documented as medical history. After the first dose, documentation of AEs shall continue until the last study follow-up visit, regardless of the relationship of the AE to study drug. Information to be collected includes type of event, date of onset, date of resolution, investigator-specified assessment of severity and relationship to study drug, seriousness, as well as any action taken.

While an AE is ongoing, changes in the severity (e.g., worsening and improving) should be noted in the source documents, but when documenting the AE, only the total duration and greatest severity should be recorded in the eCRF. AEs characterized as intermittent require documentation of onset and duration.

All drug-related (possibly, probably, or definitely related, see Section 11.4) AEs and abnormal laboratory test results reported or observed during the study must be followed to resolution (either return to baseline or within normal limits). All other AEs will be followed through the final visit indicated in Table 4, as appropriate.

AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. Preexisting conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should NOT be recorded as AEs. However, if the patient experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…"). Any improvement in condition should be documented per Section 9.10.11.

Each AE should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory test values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as an AE(s). Changes in laboratory test values or ECG parameters are only considered AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiological fluctuation). If abnormal laboratory test values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine levels in renal failure), only the diagnosis should be reported as an AE.

Elective procedures (surgeries or therapies) that were scheduled prior to the start of AE collection are not considered AEs. These elective procedures should not be recorded as AEs but should be documented in the patient's source documents as elective (e.g., elective periodontal surgery). However, if a pre-planned procedure is performed early (e.g., as an emergency) because of a worsening of the preexisting condition, the worsening of the condition should be captured as an AE.

11.7. Reporting Serious Adverse Events

Any AE the investigator considers serious according to the previously described criteria must be reported within 24 hours from the time the site personnel first learn about the event.

To report the SAE, fax or email the completed SAE form to Navitas Life Sciences (fax numbers and email address listed in Table 7) within 24 hours of awareness.

Table 7: SAE Reporting Contact Information

[redacted]

For questions regarding SAE reporting, contact your study manager, medical monitor, or Navitas Life Sciences.

Follow-Up Reports

The investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of new information, the updated follow-up SAE form, along with any supporting documentation (e.g., subject discharge summary or autopsy reports), should be faxed or emailed to Navitas Life Sciences.

The Sponsor or designee will notify regulatory agencies of any fatal or life-threatening unexpected events associated with the use of the study drug as soon as possible but no later than 7 calendar days after the initial receipt of the information. Initial notification will be followed by a written report within the timeframe established by the appropriate regulatory agency. For other SAEs that do not meet the fatal or life-threatening unexpected criteria, but are reported to be associated with the use of the study drug, Reata or designee will notify the appropriate regulatory

agencies in writing within the timeframe established by those regulatory agencies. Reata or designee will provide copies of any reports to regulatory agencies regarding serious and unexpected SAEs to the investigators for review and submission to their Institutional Review Board (IRB) or Ethics Committee (EC), as appropriate.

Principal investigators are responsible for informing their IRB/EC of any SAEs at their site. SAE correspondence with regulatory authorities or IRBs/ECs must be submitted to the Sponsor or designee for recording in the study file.

Note that the following SAE which are commonly observed in this patient population as part of CKD progression will not be reported to regulatory authorities as individual expedited report, except in unusual circumstances.

- Initiation of dialysis due to end stage kidney disease;
- Kidney transplant due to end stage kidney disease.

These events will be reviewed on a regular basis in aggregate and will be reported in an expedited manner if a safety signal is detected. Regular safety study updates will be reported to regulatory authorities according to local guidelines.

12. STATISTICS

12.1. Sample Size

With 70 patients enrolled (35 in each group), the study will have approximately 80% power to detect a difference between the two treatment groups in change from baseline in eGFR of 5.9 mL/min/1.73 m^2 for the primary endpoint at Week 12. The power calculation, which was based on a two-sided two-sample t-test, assumes the following:

- Two-sided Type I error rate of 0.05;
- Standard deviation of change from baseline in eGFR of 8 mL/min/1.73 m^2;
- A change from baseline in eGFR of approximately 5.9 mL/min/1.73 m^2;
- 15% drop-out and missing data will not be imputed.

Analysis of the primary endpoint will be based on the intent-to-treat (ITT) population and analyzed using mixed-model repeated measures (MMRM) with an unstructured covariance structure. The analysis method is expected to have at least as much power as the two-sample t-test used for study planning. Appropriate sensitivity analyses of the primary analysis will be specified in the Statistical Analysis Plan (SAP). The secondary efficacy endpoint will be tested for sufficiently large subgroups, but the study is not powered to show efficacy in the secondary efficacy endpoint.

12.2. Study Variables

12.2.1. Pharmacokinetic Variables

The pharmacokinetic variables include bardoxolone methyl plasma concentration-time data and estimated pharmacokinetic parameters.

12.2.2. Efficacy Variables

Change from baseline in eGFR will be used to determine the primary, secondary, and exploratory efficacy endpoints.

12.2.3. Safety Variables

The safety variables include results of laboratory test results (clinical chemistry, hematology, urinalysis and microscopy), vital sign measurements, ECG results, weight, AEs, and SAEs.

12.3. Statistical Analyses

A SAP detailing the analyses will be developed prior to database lock. All statistical analyses and data summaries will be performed using SAS® (Version 9.1 or higher) or other validated software. The SAP will serve as the final arbiter of all statistical analyses. Data will be summarized overall using descriptive statistics. Continuous data will be summarized with number of patients (n), mean, median, minimum, maximum, relevant quartiles, standard deviation, coefficient of variation, and geometric mean (where applicable). Categorical data will be summarized using frequency counts and percentages.

12.3.1. Primary Analysis of Efficacy

The ITT population, which includes all enrolled patients, will be used as the population for assessment of the primary efficacy endpoint.

The primary endpoint is change in eGFR at Week 12. A mixed-model repeated measures (MMRM) model will be used to compare patients randomized to bardoxolone methyl to patients randomized to placebo. The model will include change from baseline in eGFR as the dependent variable, baseline eGFR and CKD stage as covariates, patient as a random effect, and the following fixed factors: treatment group, protocol-scheduled nominal time point, and the interaction between treatment and time. Other covariates may be specified in the SAP. Time ordering is a repeated measure within patients. It is assumed that errors for different patients are independent with an unstructured covariance structure. Missing data will not be imputed for the primary analysis since all data collected will be included in the MMRM analysis. Appropriate sensitivity analyses will be performed and defined in the SAP. The secondary efficacy endpoint will be tested for sufficiently large subgroups, but the study is not powered to show efficacy in the secondary efficacy endpoint. Exploratory efficacy will be summarized descriptively.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

The study monitor, as a representative of the Sponsor, is obligated to follow the study conduct closely. In doing so, the monitor will visit the principal investigator and study facilities periodically and will maintain necessary telephone and letter contact. The monitor will maintain current knowledge of the study activity of the investigator and his/her staff through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigators and staff.

The Sponsor or designee will monitor all aspects of the study for compliance with applicable government regulation with respect to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline E6(R2): Good Clinical Practice: Consolidated Guideline and current standard operating procedures.

Each investigator is expected to make a reasonable effort to accommodate the monitor when monitoring visits are necessary and to be available during the site visit. Furthermore, the monitor should be provided direct access to source data and documents for trial-related monitoring and internet during the visit.

13.2. Audits and Inspections

Principal investigators and institutions involved in the study will permit study-related monitoring, audits, and IRB/EC review, and regulatory inspections, by providing direct access to all study records. In the event of an audit, the principal investigator agrees to allow the Sponsor, representatives of the Sponsor, the US FDA, and other relevant regulatory authorities access to all study records.

The principal investigator should promptly notify the Sponsor or designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor or designee.

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Reata may conduct a quality assurance audit of the investigator's clinical site, including IP storage facilities.

14.2. Financial Disclosure

Principal investigators and sub-investigators are required to provide financial disclosure information prior to starting the study. In addition, the principal investigator and sub-investigators must provide the Sponsor or designee with updated information, if any relevant changes occur during the course of the investigation and for one year following the completion of the study.

No potential investigator who has a vested financial interest in the success of this study may participate in this study.

14.3. Sponsor Obligations

The Sponsor or designee is not financially responsible for further testing/treatment of any medical condition that may be detected during the Screening process. In addition, in the absence of specific arrangements, the Sponsor or designee is not financially responsible for treatment of the patient's underlying disease.

14.4. Investigator Documentation

Before beginning the study, the principal investigator will be asked to comply with ICH E6(R2) and Title 21 of the Code of Federal Regulations (CFR) by providing the essential documents to the Sponsor or designee, which include but are not limited to the following:

- An original investigator-signed investigator agreement page of the protocol;
- The IRB/EC approval of the protocol;
- The IRB- or EC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardians;
- A Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572;
- Curricula vitae for the principal investigator and each sub-investigator listed on Form FDA 1572. A curricula vitae and current licensure, as applicable, must be provided. The curricula vitae must have been signed and dated by the principal investigators and sub-investigators within 2 years before study start-up to indicate the documents are accurate and current;
- Completed financial disclosure forms (Section 14.2) to allow the Sponsor or designee to submit complete and accurate certification or disclosure statements required under US Title 21 CFR 54. In addition, the investigators must provide to the Sponsor or designee a commitment to update this information promptly if any relevant changes

occur during the course of the investigation and for 1 year following the completion of the study;

- Laboratory certifications and normal ranges for any laboratories used by the site for the conduct of this study.

14.5. Clinical Study Insurance

In accordance with the respective national drug laws, the Sponsor has taken out patient liability insurance for all patients who give their consent and enroll in this study. This insurance covers potential fatalities, physical injuries, or damage to health that may occur during the clinical study.

14.6. Use of Information

All information regarding bardoxolone methyl supplied by the Sponsor to the investigator is privileged and confidential. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. Furthermore, the investigator is obligated to provide the Sponsor with complete data obtained during the study.

The information obtained from the clinical study will be used towards the development of bardoxolone methyl and may be disclosed to regulatory authorities, other investigators, corporate partners, or consultants as required.

15. ETHICS

15.1. Institutional Review Board (IRB) or Ethics Committee (EC) Review

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before study start. Each investigator must provide the Sponsor or its designee a signed and dated statement that the protocol and informed consent have been approved by the IRB/EC for that site before consenting patients. Prior to study initiation, the investigator is required to sign a protocol signature page confirming agreement to conduct the study in accordance with this protocol and to give access to all relevant data and records to the Sponsor, its designee, and regulatory authorities as required.

The IRB/EC chairperson or designee must sign all IRB/EC approvals and must identify the IRB/EC by name and address, the clinical protocol, and the date approval and/or favorable opinion was granted.

The principal investigator is responsible for obtaining reviews of the clinical research at intervals specified by the IRB/EC, but not exceeding 1 year. The principal investigator must supply the Sponsor or designee with written documentation of reviews of the clinical research.

15.2. Ethical Conduct of the Study

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (e.g., US Code of Federal Regulations Title 21, European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki. The principal investigator agrees to conduct the study in accordance with the ICH Guidance for Industry on Good Clinical Practice (GCP) ICH E6(R2) [https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf] and the principles of the Declaration of Helsinki [https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/]. The principal investigator must conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

15.3. Written Informed Consent

Because the study will be conducted under a United States Investigational New Drug Application, a signed informed consent form, in compliance with Title 21 of US CFR Part 50, will be obtained from each patient before the patient enters the study. For sites outside of the United States, the signed consent will be obtained in accord with local regulations, ICH E6 (R2), and principles of the Declaration of Helsinki. An informed consent template may be provided by the Sponsor or designee to the investigators. The consent must be reviewed by the Sponsor or designee before IRB/EC submission. Once reviewed, the consent will be submitted by the principal investigator to his or her IRB/EC for review and approval before the start of the study. If the informed consent form is revised during the course of the study, all participants affected by the revision must sign the revised IRB/EC-approved consent form.

Before enrollment, each prospective patient will be given a full explanation of the study and be allowed to read the approved informed consent form. Once the principal investigator or designee

is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing the informed consent form.

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/EC-approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Any changes to the proposed consent form suggested by the investigator must be agreed to by the Sponsor before submission to the IRB/EC, and a copy of the approved version and the notice of approval must be provided to the Sponsor's designated monitor after IRB/EC approval. The principal investigator or designee will provide a copy of the informed consent form (signed copy to be provided per applicable law) to the patient. The original form will be maintained in the patient's medical records at the site.

15.4. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the FDA or applicable regulatory authorities, or the IRB/EC.

The principal investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished confidential information disclosed to them for the purpose of the study. Prior written agreement from the Sponsor or designee must be obtained for the disclosure of any said confidential information to other parties.

15.5. Modification of the Protocol

Any changes that arise after the approval of the protocol must be documented as protocol amendments. The FDA or other applicable regulatory agencies must be notified of protocol amendments. The changes will become effective only after approval of the Sponsor, the investigator, the IRB/EC, and where necessary, the applicable regulatory agency. In cases when the protocol is modified to enhance patient safety, changes may be implemented, and the amendment must be immediately submitted to the IRB/EC.

The investigator is responsible for informing the IRB/EC of all problems involving risks to patients according to national legislation. In case of urgent safety measures, the Sponsor will immediately notify the investigators and relevant regulatory agencies, including FDA in accord with 21 CFR 312.32.

15.6. Protocol Deviations

The investigator and site staff are required to follow the study procedures and schedules as documented in the protocol. If a protocol deviation occurs, the principal investigator or designee must document the deviation in the Deviation Log Form in the clinical database. The IRB/EC

must be notified of protocol deviations in a timely manner by the principal investigator or designee as appropriate. Protocol deviations will be reviewed by the responsible monitor during monitoring visits, and those observations will be communicated to the investigator. Protocol deviations will be reviewed and any that are a serious breach of GCP and the protocol will be reported to the relevant regulatory agency, as required.

Protocol waivers are not allowed. If there is an immediate hazard to a patient, the principal investigator may deviate from the protocol using his/her best medical judgement to ensure the patient's safety. If such a deviation occurs, the site must notify the Sponsor and IRB/EC within 48 hours.

16. DATA HANDLING AND RECORDKEEPING

16.1. Retention of Records

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application submission or 2 years after formal discontinuation of the clinical development of the investigational product. If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

16.2. Case Report Forms

All case report form data will be entered in paper or electronic forms at the investigational site. A 21 CFR Part 11 compliant Electronic Data Capture system (EDC) will be used to capture data electronically for all patients enrolled in the study.

17. PUBLICATION POLICY

The Sponsor supports communication and publication of study results whatever the findings of the study.

The Sponsor reserves the right to review all planned communications and manuscripts based on the results of this study. This reservation of the right is not intended to restrict or hinder publication or any other dissemination of study results, but to allow the Sponsor to confirm the accuracy of the data, to protect proprietary information, and to provide comments based on information that may not yet be available to the study investigators. The Sponsor also encourages disclosure of any conflict of interest from all authors or investigators when manuscripts are submitted for publication. Those individuals who have contributed greatly to this study, including lead external advisors and select principal investigators, may serve on any potential publications committee for the study.

18. LIST OF REFERENCES

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19. APPENDIX

APPENDIX 1

Prognosis of CKD by eGFR and Albuminuria Categories: KDIGO 2012 (Levin, 2014)

GFR categories (ml/min per 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	⩾90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

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