RTA 402

402-C-1702

[redacted]

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

VERSION 1.0 –17 AUGUST 2017

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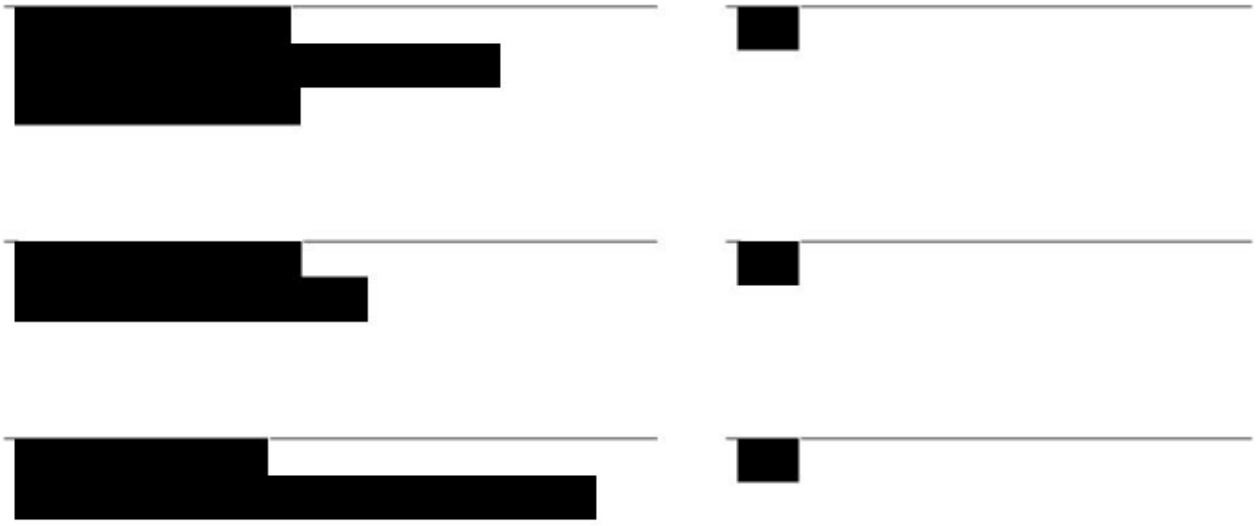
SPONSOR APPROVAL AND SIGNATURE PAGE



INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for bardoxolone methyl. I have read the 402-C-1702 clinical study protocol and agree to conduct the study as outlined. 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 Study Manager	[redacted]	[redacted]
Medical Monitor	[redacted]	[redacted]
SAE Reporting	[redacted]	

2. SYNOPSIS

Name of Sponsor/Company:
Reata Pharmaceuticals, Inc.

Name of Investigational Product:
Bardoxolone methyl

Title of Study:
A Phase 2 Trial of the Safety and Efficacy of Bardoxolone Methyl in Patients with Rare Chronic Kidney Diseases

Study center(s): Up to 60 study centers

Studied period: 1 year Estimated date first patient enrolled: December 2017 Estimated date last patient completed: December 2018	**Phase of development:** 2

Objectives:

For patients within each rare chronic kidney disease (CKD) cohort enrolled in this study, the primary objectives are as follows:

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

Methodology:

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

Patients will receive bardoxolone methyl throughout the study and the maximum bardoxolone methyl dose will be determined by baseline proteinuria status. Patients with macroalbuminuria ($300 \text{ mg/g} < \text{ACR} \leq 2500 \text{ mg/g}$) at the Screen B visit will account for up to approximately 50% of patients enrolled within each cohort. Patients with baseline $\text{ACR} \leq 300$ mg/g will be titrated to a maximum dose of 20 mg, and patients with baseline $\text{ACR} > 300$ mg/g will be titrated to a maximum dose of 30 mg. 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 ACR >300 mg/g) unless contraindicated clinically and approved by the medical monitor. Dose de-escalation is permitted during the study if indicated clinically, and subsequent dose re-escalation is also permitted to meet the dosing objective of the highest tolerated dose. Please refer to Section 7.3.1 for additional details on dose escalation and dose de-escalation.

All patients in the study will follow the same visit and assessment schedule. Following randomization on Day 1, patients will be scheduled to be assessed during treatment at Weeks 1, 2, 4, 6, 8, and 12, and by telephone contact on Days 3, 10, 21, 31, 38, and 45. Patients will also be scheduled to be assessed at an in-person follow-up visit at Week 16, four weeks after the end of treatment.

Number of patients (planned):

Each cohort will enroll approximately 25 patients, for a total of approximately 100 patients in the trial.

Diagnosis and main criteria for inclusion:

1. Male and female patients 18 ≤ age ≤ 65 upon study consent;
2. Screening eGFR (average of Screen A and Screen B eGFR values) ≥ 30 and ≤ 90 mL/min/1.73 m^2. The two eGFR values collected at Screen A and Screen B visits used to determine eligibility must have a percent difference ≤ 25%;
3. Albumin to creatinine ratio (ACR) ≤ 2500 mg/g at Screen B visit;
4. If receiving an angiotensin-converting enzyme (ACE) inhibitor and/or an angiotensin II receptor blocker (ARB), patients should be prescribed the maximally tolerated labeled daily dose (MTLDD), as defined in Section 9.1.7, for at least 6 weeks prior to the Screen A visit. The dosage of ACE inhibitor and/or ARB should remain the same throughout the remainder of the study (*i.e.*, no change in dosage or medication), and any potential changes should be discussed with the medical monitor. Patients not taking an ACE inhibitor and/or ARB because of a medical contraindication may be eligible if they have discontinued treatment at least 8 weeks prior to the Screen A visit (these patients must be discussed with the medical monitor prior to enrollment);
5. For patients enrolling in T1D Cohort:
    a. Diagnosis of type 1 diabetes confirmed by fasting C-peptide level. Diagnosis must have been made ≤ 35 years of age;
    b. Prescribed stable dose of insulin to maintain adequate glucose control for at least 6 months prior to the Screen A visit;
6. For patients enrolling in IgAN Cohort:
    a. Biopsy-confirmed IgA nephropathy;
7. For patients enrolling in FSGS Cohort:
    a. Biopsy-confirmed FSGS that is not due to known secondary causes including morbid obesity, decreased renal mass, viral infections, drug-induced nephrotoxicity, or prior history of vasculitis;
8. For patients enrolling in ADPKD Cohort:
    a. Genetic confirmation of PKD1 mutation;
9. Adequate bone marrow reserve and organ function at the Screen A visit as follows:
    a. Hematologic: Absolute neutrophil count > 1.5 x 10^9/L, platelets > 100 x 10^9/L, hemoglobin (Hgb) ≥ 9 g/dL;
    b. Hepatic: Total bilirubin (TBL) ≤ 1.5X the upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 1.5X ULN ;
10. Able to swallow capsules;
11. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures;
12. 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.

Major exclusion criteria:

1. Prior exposure to bardoxolone methyl;
2. Kidney or any other solid organ transplant recipient or a planned transplant during the study;
3. B-type natriuretic peptide (BNP) level > 200 pg/mL at Screen A visit;
4. Acute dialysis or acute kidney injury within 12 weeks prior to Screen A visit or during Screening;
5. Serum albumin < 3 g/dL at Screen A visit;
6. Systemic immunosuppression for more than 2 weeks, cumulatively, within the 12 weeks prior to randomization or anticipated need for immunosuppression during the study. Patients with IgAN or FSGS that are receiving prednisone at doses ≤ 10 mg/day are eligible for enrollment in the IgAN or FSGS cohorts, but doses must be stable for 30 days prior to Screen A visit and should be anticipated to remain the same throughout the study. Refer to Section 9.3.1 for additional details;
7. For patients enrolling in IgAN Cohort:
    a. Systemic manifestations of Henoch-Schonlein purpura within 1 year prior to Screen A visit;
    b. Have used belimumab, eculizumab, or rituximab within 6 months prior to Screen A visit;
8. For patients enrolling in ADPKD Cohort:
    a. Receiving tolvaptan;
9. Cerebrovascular event (stroke, transient ischemic attack) or aneurysm within 6 months prior to Screen A visit or during Screening;
10. History of clinically significant left-sided heart disease and/or clinically significant cardiac disease, including but not limited to any of the following:
    a. Clinically significant congenital or acquired valvular disease;
    b. Left ventricular ejection fraction < 40% (based on echocardiogram performed at Screen A visit or within 6 months prior to Day 1);
    c. Pericardial constriction (based on echocardiogram performed at Screen A visit or within 6 months prior to Day 1);
    d. Restrictive or congestive cardiomyopathy (based on echocardiogram performed at Screen A visit or within 6 months prior to Day 1);
    e. Symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or angina);
    f. History of hospitalization for heart failure;
    g. Cardiac insufficiency, defined as New York Heart Association Class > 2;
    h. History of atrial fibrillation;
    i. History of unstable arrhythmias;
11. Uncontrolled systemic hypertension as evidenced by sitting systolic blood pressure (BP) > 160 mm Hg or sitting diastolic BP > 100 mm Hg at Screen A visit after a period of rest;
12. Systolic BP < 90 mm Hg at Screen A visit after a period of rest;
13. History of malignancy within 2 years prior to Screen A visit, with the exception of localized skin or cervical carcinomas;
14. Uncontrolled diabetes (HbA1c > 10.0%) at Screen A visit;

15. Untreated or uncontrolled active bacterial, fungal, or viral infection;
16. Participation in other interventional clinical studies within 30 days prior to Day 1;
17. Unwilling to practice acceptable methods of birth control (both males who have partners of child-bearing potential and females of childbearing potential) during Screening, while taking study drug, and for at least 30 days after the last dose of study drug is ingested;
18. Women who are pregnant or breastfeeding;
19. Known hypersensitivity to any component of the study drug;
20. Any abnormal laboratory level that, in the opinion of the investigator, would put the patient at risk by trial enrollment;
21. Patient is, in the opinion of the investigator, unable to comply with the requirements of the study protocol or is unsuitable for the study for any reason.

Investigational product, dosage, and mode of administration:

Bardoxolone methyl will be administered orally at 5, 10, 20, or 30 mg.

Duration of treatment:

Bardoxolone methyl will be administered through Week 12.

Reference therapy, dosage and mode of administration:

Not applicable.

Criteria for evaluation:

Efficacy: eGFR, [redacted]

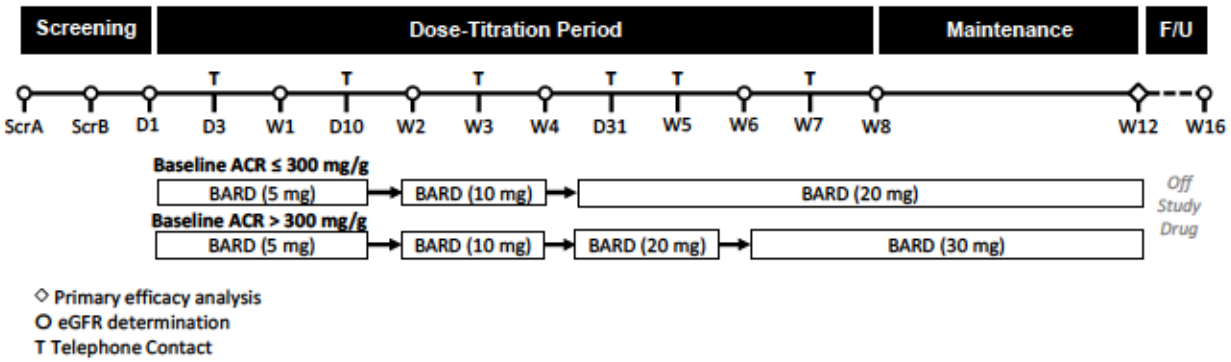
Safety: Results of laboratory results (clinical chemistry, hematology, urinalysis), vital sign measurements, electrocardiogram (ECG) results, weight, adverse events (AEs), and serious adverse events (SAEs).

Statistical methods:

Sample size:

[redacted]

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



◇ Primary efficacy analysis
O eGFR determination
T Telephone Contact

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ACE	Angiotensin converting enzyme
ACR	Albumin to creatinine ratio
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARB	Angiotensin II receptor blocker
AST	Aspartate aminotransferase
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	Blood Pressure
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations (US)
[redacted]	[redacted]
CK	Creatine kinase
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CrCl	Creatinine clearance
CTM	Clinical trial material
CV	Cardiovascular
EC	Ethics Committee
eCRF	Electronic case report form
ECG	Electrocardiogram
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EoT	End-of-treatment
ERA	Endothelin receptor antagonist
ESRD	End stage renal disease

Abbreviation or Specialist Term	Explanation
FDA	Food and Drug Administration (US)
FSGS	Focal segmental glomerulosclerosis
F/U	Follow-up
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase
HbA1c	Hemoglobin A1c
HCV	Hepatitis C virus
HDPE	High-density polyethylene
Hgb	Hemoglobin
ICH	International Conference on Harmonization
IgA	Immunoglobulin A
IgAN	Immunoglobulin A nephropathy
IGF-1	Insulin-like growth factor-1
IKKβ	Inhibitor of nuclear factor kappa β kinase beta subunit
IMP	Investigational medicinal products
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
J2R	Jump to reference
KDIGO	Kidney Disease: Improving Global Outcomes
Keap1	Kelch-like ECH associated protein-1
K_f	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
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B-cells
Nrf2	Nuclear factor (erythroid-derived 2)-related factor 2

Abbreviation or Specialist Term	Explanation
NT-Pro BNP	N-Terminal Pro-Brain Natriuretic Peptide
PBO	Placebo
[redacted]	[redacted]
PH	Pulmonary hypertension
PK	Pharmacokinetic
PKD1	Polycystic kidney disease 1
QTc	Corrected QT interval
RBC	Red blood cell
REML	Restricted maximum likelihood
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SAE	Serious adverse event
SAP	Statistical analysis plan
T2D	Type 2 diabetes
TBL	Total bilirubin
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of child bearing potential

5. INTRODUCTION

Bardoxolone methyl and its analogs are oleanolic acid-derived synthetic triterpenoid compounds that potently induce the Nrf2-Keap1 pathway (Wu, 2011; Rojas-Rivera, 2012). Through interaction with the Nrf2 repressor molecule, Keap1, bardoxolone methyl and its analogs promote translocation of Nrf2 to the nucleus, where Nrf2 binds to antioxidant response elements in the promoter region of its target genes, leading to induction of many antioxidant and cytoprotective enzymes and related proteins (Lee, 2009; Dinkova-Kostova, 2005). Bardoxolone methyl and its analogs are also potent inhibitors of the NF-κB inflammatory pathway through both direct (*i.e.*, inhibition of IKKβ kinase activity) and indirect mechanisms (*i.e.*, detoxification of reactive oxygen species) (Osburn, 2008). Because of this dual mechanism of action, bardoxolone methyl and its analogs are hypothesized to have potential therapeutic relevance in a variety of disease settings involving oxidative stress and inflammation.

Multiple studies validate the renal protective effect of Nrf2 activation. In contrast, Nrf2 gene ablation intensifies inflammation, oxidative stress, and renal injury in preclinical models. Nrf2-knockout mice exhibit a lupus-like autoimmune nephritis (Yoh, 2001) and histologic analyses of kidney tissue show enlarged glomeruli, mesangial cell proliferation, thickening of the glomerular basement membrane, and glomerulosclerosis (Ma, 2006). Similarly, Nrf2-knockout mice are more susceptible to nephrotoxic insults and develop more severe renal impairment. Mechanistic studies demonstrate that Nrf2-mediated protection against these effects is at least partially through inhibition of transforming growth factor-β1 and reduction of extracellular matrix production (Jiang, 2010). Collectively, these data establish that Nrf2 plays an important role in maintaining the function and structure of the kidney and Nrf2 activation offers protection from renal injury and dysfunction.

Chronic kidney disease (CKD) is a disease of decreased kidney function that can progress to kidney failure and end-stage renal disease (ESRD). Rare forms of CKD include CKD associated with type 1 diabetes (T1D), IgA nephropathy (IgAN), focal segmental glomerulosclerosis (FSGS), and autosomal polycystic kidney disease (ADPKD). Although GFR decline is initiated by different pathogenic stimuli in T1D CKD, IgAN, FSGS, and ADPKD, the pathogenic role of inflammatory processes in disease progression and declining renal function is similar across each of these diseases. Hypoglycemia in T1D, abnormal immunoglobulin A (IgA) deposition and clearance in IgAN, segmental scarring in FSGS, and renal cyst formation in ADPKD, all trigger a cascade of pathological inflammatory processes that, over prolonged periods, result in oxidative stress, mesangial matrix expansion, glomerulosclerosis and fibrosis, decreased surface area for filtration, and reduced renal function.

More specifically, the chronic activation of pro-inflammatory pathways in kidney cells promotes GFR loss by at least three mechanisms: (a) in glomerular endothelial cells, inflammation-associated reactive oxygen species (ROS) induce endothelial nitric oxide synthase (eNOS) uncoupling and the production of peroxynitrite, which depletes vasodilatory nitric oxide resulting in loss of endothelial function and reduced glomerular surface area for filtration (*i.e.*, decreases in the ultrafiltration coefficient, K_f); (b) inflammation-associated ROS induce a contractile response in mesangial cells resulting in reduced K_f and GFR; and (c) ROS-mediated activation of inflammatory pathways leads to fibrosis, promoting structural alterations in the mesangium and

glomerular basement membrane thickening that contributes to GFR decline. GFR decline from these processes inevitably leads to ESRD.

Through Nrf2 activation and inhibition of NF-κB, bardoxolone methyl and closely related structural analogs have been shown to improve renal function, reduce inflammation, and prevent structural injury in multiple models of renal injury and disease (Tanaka, 2008; Zoja, 2010; Wu, 2011; Aminzadeh, 2013; Ding, 2013). In particular, several of these studies elucidate the effects of bardoxolone methyl and closely related analogs on the underlying disease processes that promote reduced GFR. Specifically, bardoxolone methyl and analogs reverse endothelial dysfunction (Ferguson, 2010) and mesangial cell contraction, thereby increasing glomerular surface area (K_f) and GFR (Ding, 2013). Further, data from animal models of chronic renal disease demonstrate that the compounds are anti-fibrotic and have protective effects on the renal interstitium in response to high protein (Zoja, 2010) and pressure overload in the setting of hyperfiltration (Aminzadeh, 2013).

Bardoxolone methyl has consistently improved parameters of renal function in multiple clinical studies in patients with CKD associated with type 2 diabetes (T2D), cancer, and pulmonary hypertension (PH), with significant increases in inulin clearance, creatinine clearance, and estimated eGFR. The changes in eGFR also correlate in reductions in other parameters such as blood urea nitrogen (BUN), uric acid, and phosphate, and not associated with validated markers of renal injury, providing corroboration that bardoxolone methyl treatment is associated with improvements in kidney function.

The profile of eGFR increases with bardoxolone methyl reflects its multiple protective and anti-inflammatory effects. Early improvements in eGFR evident within the first 4 weeks of bardoxolone methyl treatment are likely attributed to the reversal of acute, dynamic inflammation-mediated processes such endothelial dysfunction and mesangial cell contraction resulting in glomerular filtration surface area increases. These increases in eGFR are sustained for patients treated with bardoxolone methyl for up to one year, with retained eGFR increases from baseline event after withdrawal of drug treatment. The magnitude and durability of these changes are quite different from the pattern observed with eGFR increases due to intraglomerular pressure or hyperfiltration. Over 400 patients with T2D CKD have been treated with bardoxolone methyl for 1 year or longer, with no evidence of renal toxicity, as assessed by validated markers of renal injury, proportion of patients with clinically meaningful loss of eGFR, renal SAEs, and ESRD. Thus, the collective data support that bardoxolone methyl may have disease-modifying effects in the kidney (*e.g.*, reversal of mesangial expansion and interstitial fibrosis) that are beneficial and not deleterious. On the basis of these results, bardoxolone methyl is also currently being evaluated in a Phase 2/3 study in patients with Alport syndrome.

In patients with T1D CKD, IgAN, FSGS, and ADPKD, the potential impact of a sustained eGFR increase with bardoxolone methyl treatment is clinically meaningful and could provide a multi-year delay in disease progression to ESRD.

5.1. Clinical Experience with Bardoxolone Methyl

Approximately 1950 individuals have been exposed to bardoxolone methyl. Sixteen studies have been completed (seven in patients with CKD who also had type 2 diabetes, four in non-CKD indications, and five in healthy subjects), two studies are ongoing in patients with PH, and one study is ongoing in patients with Alport syndrome.

5.1.1. Efficacy

As seen in Table 3, improvements in renal function, including eGFR, creatinine clearance, and inulin clearance, have been observed with bardoxolone methyl treatment in multiple clinical studies, including those in T2D CKD, cancer, and 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 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. 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 Type 2 diabetes. A total of 2185 patients were randomized 1:1 to once-daily administration of the amorphous SDD 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 end-Stage renal disease (ESRD; need for chronic dialysis, renal transplantation, or renal death) or cardiovascular (CV) 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 Study 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 renal function, resulting in sustained eGFR improvement after withdrawal of drug.

Notably, Reata's Asian development partner, Kyowa Hakko Kirin, demonstrated that bardoxolone methyl treatment resulted in a significant improvement in GFR in Japanese patients with CKD and type 2 diabetes. Improvements in other measures of renal function, including BUN, uric acid, and phosphorus, have also been consistently observed, providing further evidence that observed changes in eGFR reflect true improvements in kidney function. Mostly recently, bardoxolone methyl has been shown to significantly increase eGFR after 12 weeks of treatment in a Phase 2 open-label study in patients with Alport syndrome (Study 402-C-1603).

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/1.73m^2)[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	108	16 weeks	6.6 (inulin GFR) (p=0.008 vs PBO)
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 m^2)	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.

[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 Cohorts 1 and 2.

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 (ERAs) 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 type 2 diabetes. The overall increased risk for fluid overload and heart failure events with bardoxolone methyl appeared to be limited to the first three to four weeks after initiation of treatment. Elevated 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.

In a Phase 2 dose-ranging study of the efficacy and safety of bardoxolone methyl in patients with pulmonary hypertension (LARIAT), risk mitigation procedures were employed 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. To date, the risk for acute fluid overload AEs with bardoxolone methyl in late-stage CKD patients has not been observed in PH patients.

5.1.2.2. Transaminase and Gamma-glutamyl Transpeptidase (GGT) Elevations

In clinical studies of bardoxolone methyl, almost all patients had increases of transaminase 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 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, transaminase elevations were mild, but approximately 4% to 11% of patients experienced an elevation greater than 3X the 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 GGT, a known Nrf2 target gene. In clinical studies, low level GGT elevations during treatment were common, mild, and typically lasted longer than ALT/AST elevations. Bilirubin levels in patients experiencing transaminase 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 AE in clinical trials of bardoxolone methyl in patients with CKD who also had type 2 diabetes. 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 have also been reported in bardoxolone methyl-treated PH patients but at lower incidences than that observed in prior CKD studies. Moreover, the incidence of muscle spasms is similar to that observed in placebo-treated PH patients. 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), 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 who also had type 2 diabetes. 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.

Bardoxolone methyl-treated PH patients have also had decreases in weight, with mean weight decreases of approximately 3 kg versus placebo at Week 16. Weight loss in PH patients has not coincided with reports of decreased appetite or anorexia AEs.

5.1.2.5. Hypomagnesaemia

Hypomagnesaemia has not been reported in PH patients to date, but was reported as an AE for 15.5% of patients with CKD who also had type 2 diabetes who received bardoxolone methyl. The AE of hypomagnesaemia (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 hypomagnesaemia and either gastrointestinal AEs or cardiac AEs, including cardiac dysrhythmias and prolonged 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.

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 and type 2 diabetes. 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. 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.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objectives

For patients within each cohort enrolled in this study, the primary objectives are as follows:

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

6.2. Primary Efficacy Endpoint

- Change from baseline in eGFR at Week 12.

[redacted]

6.4. Safety Endpoints

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

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

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

Patients will receive bardoxolone methyl throughout the study and the maximum bardoxolone methyl dose will be determined by baseline proteinuria status. Patients with macroalbuminuria (300 mg/g < ACR ≤ 2500 mg/g) at the Screen B visit will account for up to approximately 50% of patients enrolled within each cohort. Patients with baseline ACR ≤ 300 mg/g will be titrated to a maximum dose of 20 mg, and patients with baseline ACR > 300 mg/g will be titrated to a maximum dose of 30 mg. Patients will start with once-daily dosing at 5 mg and will dose-escalate to 10 mg at Week 2, to 20 mg at Week 4, and then to 30 mg at Week 6 (only if baseline ACR >300 mg/g) unless contraindicated clinically and approved by the medical monitor. Dose de-escalation is permitted during the study if indicated clinically, and subsequent dose re-escalation is also permitted to meet the dosing objective of the highest tolerated dose. Please refer to Section 7.3.1 for additional details on dose escalation and dose de-escalation.

All patients in the study will follow the same visit and assessment schedule. Following randomization on Day 1, patients will be scheduled to be assessed during treatment at Weeks 1, 2, 4, 6, 8, and 12, and by telephone contact on Days 3, 10, 21, 31, 38, and 45. Patients will also be scheduled to be assessed at an in person follow-up visit at Week 16, four weeks after the end of treatment.

7.2. Number of Patients

Each cohort will enroll approximately 25 patients, for a total of approximately 100 patients in the trial.

7.3. Treatment Assignment and Rationale

All patients will receive bardoxolone methyl throughout the study. 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 type 2 diabetes and CKD, Reata has concluded that larger bardoxolone methyl doses may be required to have an optimal effect on eGFR in patients with macroalbuminuria. Specifically, eGFR improvements in patients with microalbuminuria 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 ACR ≤ 300 mg/g and a maximum dose of 30 mg for patients with ACR > 300 mg/g, as described

below. 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.

7.3.1. Dose Escalation

Patients will start with once-daily dosing of bardoxolone methyl at 5 mg and will dose-escalate to 10 mg at Week 2, to 20 mg at Week 4, and then to 30 mg at Week 6 (only if baseline ACR >300 mg/g) unless contraindicated clinically and approved by the medical monitor (Table 4). The dosing objective is to titrate patients to the maximum dose determined by baseline ACR, and maintain the maximum dose after initial dose-titration. The investigator should discuss any reason for not dose-escalating at Weeks 2 and 4 with the medical monitor. Dose escalation at subsequent visits is permitted to meet the dosing objective.

Table 4: Bardoxolone Methyl Dose by Study Visit and Albuminuria Status

Baseline ACR	Day 1	Week 2	Week 4	Week 6 to Week 12
ACR ≤ 300 mg/g	5 mg	10 mg	20 mg	20 mg
300 mg/g < ACR ≤ 2500 mg/g	5 mg	10 mg	20 mg	30 mg

7.3.2. 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 prior to changing dose and must be documented. After dose de-escalation, patients should return for an unscheduled office visit within 4 weeks (± 3 days) to collect clinical chemistry and to perform the assessments detailed in Section 9.7.

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 NT-proBNP. Unscheduled visits due to dose escalation should also include assessments detailed in Section 9.7.

7.4. Criteria for Study Termination

Although the Sponsor intends to complete the study, the Sponsor reserves the right to discontinue a cohort or 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.

7.5. Schedule of Assessments

Table 5 lists the overall schedule of assessments for the study.

Table 5: Schedule of Assessments

Assessment	Screen A[a]	Screen B[b]	Day 1[c]	Wk 1 (Phone) Day 3±2	Wk 1 Day 7±3	Wk 2 (Phone) Day 10±2	Wk 2 Day 14±3	Wk 3 (Phone) Day 21±2	Wk 4 Day 28±3	Wk 4 (Phone) Day 31±2	Wk 5 (Phone) Day 38±2	Wk 6 Day 42±3	Wk 7 (Phone) Day 45±2	Wk 8 Day 56±3	Wk 12 or EoT[d] Day 84±3	Wk 16 or F/U Day 112±3
Informed consent	X															
Inclusion/ exclusion	X		X[e]													
Demographics and baseline disease characteristics	X															
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical history	X															
Height	X															
Weight in clinic/BMI	X		X		X		X		X			X		X	X	X
Weight at home			X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense weight diary			X				X		X			X		X		
Collect/review weight diary				X	X	X	X	X	X	X	X	X	X	X	X	
ECG	X														X	X
Echocardiogram[f]	X															
Vital sign measurements	X		X		X		X		X			X		X	X	X
Physical exam	X		X		X		X		X			X		X	X	X
Pregnancy test for WOCBP[g]	X	X	X						X					X	X	X
Study drug administration			----------X----------													
Dispense study drug			X				X		X			X		X		
Collect study drug							X		X			X		X	X	
Telephone contact				X		X		X		X	X		X			
Adverse event collection			X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Kidney biopsy[i]	X															
Fasting C-peptide level[j]	X															
Genetic testing[k]	X															
Clinical chemistry (incl. eGFR)	X	X	X		X		X		X			X		X	X	X
BNP and NT-proBNP	X		X		X		X		X			X		X	X	X
IGF-1 and serum ketones	X		X		X		X		X			X		X	X	X
Hematology	X		X				X		X			X		X	X	X
Urinalysis and microscopy	X		X				X		X			X		X	X	X
Urine collection for ACR[l]		X	X						X					X	X	X
[redacted]															X	X
[redacted]															X	X
Virus serology	X															
PK samples[m]															X	

[a] Total Screening period should not exceed 6 months.
[b] Screen B visit should be no more than 30 days prior to Day 1.
[c] Day 1 is the day of administration of the first dose. **On Day 1, all procedures should be performed before study drug administration.**
[d] Patients who terminate from the study prior to the Week 12 study visit should be brought back to the clinic as soon as possible for early termination assessments (*i.e.*, end-of-treatment visit) as well as a follow-up visit 4 weeks later.
[e] Screening eligibility procedures do not need to be repeated on Day 1; however, a review of any changes in eligibility criteria should be evaluated prior to Day 1 procedures, and a urine pregnancy test should be performed for WOCBP.
[f] An echocardiogram performed at the Screen A visit or within 6 months prior to Day 1 may be used to determine eligibility.
[g] A serum pregnancy test will be performed at the Screen A visit for WOCBP or at any point in time if a pregnancy is suspected. All other pregnancy assessments will be urine pregnancy tests.
[h] AE assessments on Day 1 should be performed following study drug administration.
[i] Only patients enrolling in the IgA nephropathy cohort or the FSGS cohort are required to have a kidney biopsy. Patients with definitive diagnosis of IgA nephropathy or FSGS from previous biopsy will not have a kidney biopsy as part of the study, but must provide diagnosis documentation from previous kidney biopsy for eligibility.
[j] Only patients enrolling in the T1D cohort are required to have fasting C-peptide levels assessed. Patients should be instructed to fast prior to study visit.
[k] Only patients enrolling in the ADPKD disease cohort are required to have genetic testing. Patients with confirmed PKD1 mutations from previous genetic testing will not have genetic testing performed as part of the study, but must provide documentation of genetic mutation for eligibility.
[l] Albumin to creatinine ratio will be measured by first morning void spot urine collection. Appropriate containers for the collection will be provided to the patient at the visit prior to collection.
[m] Patients must be instructed to not take their study drug prior to coming to the clinic for visits when PK samples will be collected. Patients must administer the study drug dose in the clinic on PK sample collection visits after the 0 hour PK blood sample is collected. Patients will have blood samples for PK analysis drawn just prior to (0 hour) and after (2 and 4 hours) dose administration.

Abbreviations: EoT= end-of-treatment; ECG = electrocardiogram, F/U = follow-up; PK = pharmacokinetic, WOCBP = women of child-bearing potential

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Inclusion Criteria

Diagnosis and main criteria for inclusion:

1. Male and female patients 18 ≤ age ≤ 60 upon study consent;
2. Screening eGFR (average of Screen A and Screen B eGFR values) ≥ 30 and ≤ 90 mL/min/1.73 m^2. The two eGFR values collected at Screen A and Screen B visits used to determine eligibility must have a percent difference ≤ 25%;
3. Albumin to creatinine ratio (ACR) ≤ 2500 mg/g at Screen B visit;
4. If receiving an angiotensin converting enzyme (ACE) inhibitor and/or an angiotensin II receptor blocker (ARB), patients should be prescribed the maximally tolerated labeled daily dose (MTLDD), as defined in Section 9.1.7, for at least 6 weeks prior to the Screen A visit. The dosage of ACE inhibitor and/or ARB should remain the same throughout the remainder of the study (*i.e.*, no change in dosage or medication), and any potential changes should be discussed with the medical monitor. Patients not taking an ACE inhibitor and/or ARB because of a medical contraindication may be eligible if they have discontinued treatment at least 8 weeks prior to the Screen A visit (these patients must be discussed with the medical monitor prior to enrollment);
5. For patients enrolling in T1D Cohort:
   a. Diagnosis of type 1 diabetes confirmed by fasting C-peptide level. Diagnosis must have been made ≤ 35 years of age;
   b. Prescribed stable dose of insulin to maintain adequate glucose control for at least 6 months prior to the Screen A visit;
6. For patients enrolling in IgAN Cohort:
   a. Biopsy-confirmed IgA nephropathy;
7. For patients enrolling in FSGS Cohort:
   a. Biopsy-confirmed FSGS that is not due to known secondary causes including morbid obesity, decreased renal mass, viral infections, drug-induced nephrotoxicity, or prior history of vasculitis;
8. For patients enrolling in ADPKD Cohort:
   a. Genetic confirmation of PKD1 mutation;
9. Adequate bone marrow reserve and organ function at the Screen A visit as follows:
   a. Hematologic: Absolute neutrophil count > 1.5 x 10^9/L, platelets > 100 x 10^9/L, hemoglobin (Hgb) ≥ 9 g/dL;
   b. Hepatic: Total bilirubin (TBL) ≤ 1.5X the upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 1.5X ULN;
10. Able to swallow capsules;

11. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures;
12. 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 patient-mandated procedures.

8.2. Patient 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. Kidney or other solid organ transplant recipient or a planned transplant during the study;
3. B-type natriuretic peptide (BNP) level >200 pg/mL at Screen A visit;
4. Acute dialysis or acute kidney injury within 12 weeks prior to Screen A visit or during Screening;
5. Serum albumin < 3 g/dL at Screen A visit;
6. Systemic immunosuppression for more than 2 weeks, cumulatively, within the 12 weeks prior to randomization or anticipated need for immunosuppression during the study. Patients with IgAN or FSGS that are receiving prednisone at doses ≤ 10 mg/day are eligible for enrollment in the IgAN or FSGS cohorts, but doses must be stable for 30 days prior to Screen A visit and should be anticipated to remain the same throughout the study. Refer to Section 9.3.1 for additional details;
7. For patients enrolling in IgAN Cohort:
    a. Systemic manifestations of Henoch-Schonlein purpura within 1 year prior to Screen A visit;
    b. Have used belimumab, eculizumab, or rituximab within 6 months prior to Screen A visit;
8. For patients enrolling in ADPKD Cohort:
    a. Receiving tolvaptan;
9. Cerebrovascular event (stroke, transient ischemic attack) or aneurysm within 6 months prior to Screen A visit or during Screening;
10. History of clinically significant left-sided heart disease and/or clinically significant cardiac disease, including but not limited to any of the following:
    a. Clinically significant congenital or acquired valvular disease;
    b. Left ventricular ejection fraction < 40% (based on echocardiogram performed at Screen A visit or within 6 months prior to Day 1);
    c. Pericardial constriction (based on echocardiogram performed at Screen A visit or within 6 months prior to Day 1);
    d. Restrictive or congestive cardiomyopathy (based on echocardiogram performed at Screen A visit or within 6 months prior to Day 1);

e. Symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or angina);

f. History of hospitalization for heart failure;

g. Cardiac insufficiency, defined as New York Heart Association Class >2;

h. History of atrial fibrillation;

i. History of unstable arrhythmias;

11. Uncontrolled systemic hypertension as evidenced by sitting systolic blood pressure (BP) > 160 mm Hg or sitting diastolic BP > 100 mm Hg at Screen A visit after a period of rest;
12. Systolic BP < 90 mm Hg at Screen A visit after a period of rest;
13. History of malignancy within 2 years prior to Screen A visit, with the exception of localized skin or cervical carcinomas;
14. Uncontrolled diabetes (HbA1c > 10.0%) at Screen A visit;
15. Untreated or uncontrolled active bacterial, fungal, or viral infection;
16. Participation in other interventional clinical studies within 30 days prior to Day 1;
17. Unwilling to practice acceptable methods of birth control (both males who have partners of 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;
18. Women who are pregnant or breastfeeding;
19. Known hypersensitivity to any component of the study drug;
20. Any abnormal laboratory level that, in the opinion of the investigator, would put the patient at risk by trial enrollment;
21. Patient is, in the opinion of the investigator, unable to comply with the requirements of the study protocol or is unsuitable for the study for any reason;

8.3. Screening Period

The screening period must not exceed 6 months. The Screen B visit should be no more than 30 days prior to Day 1.

8.4. Patient Re-Screening

Patients that screen fail may repeat the Screening procedures to qualify for the study with approval from the medical monitor.

8.5. Patient Discontinuation and Termination

Patients have the right to discontinue study drug or withdraw from the study 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 prior to study drug discontinuation or withdrawing a patient from the study. The reason for a patient's

discontinuation from study drug or study termination will be recorded in the electronic case report form (eCRF).

8.5.1. Patient Discontinuation Criteria

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

- Occurrence of an AE or change in medical status that leads the investigator to be concerned about the patient's welfare
- Administrative reasons (*e.g.*, inability to continue)
- Sponsor termination of the study
- Voluntary withdrawal
- Females who become pregnant during the study

Patients must discontinue study drug if any of the following occur.

- ALT or AST > 8X ULN;
- ALT or AST > 5X ULN for more than two weeks;
- ALT or AST > 3X ULN and (total bilirubin > 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%).

Patients who are discontinued from study drug should still continue in the study, complete all study visits, and undergo all scheduled study assessments, if possible.

8.5.2. Patient Termination Criteria

Termination refers to a patient's stopping study drug and all study assessments and visits. Reasons for study termination include the following:

- Loss to follow-up
- Death
- Withdrawal of consent

Every reasonable effort should be made to contact patients who do not return for a scheduled visit. The investigator should inquire about the reason for withdrawal, 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.

9. TREATMENT OF PATIENTS

9.1. Select Management Guidelines

The following guidelines apply to the management of study participants:

9.1.1. Management of Fluid Status

Specific risk mitigation procedures will be employed to reduce the potential for bardoxolone methyl-induced fluid overload. These procedures include exclusion of patients with any severe renal disease, defined as an eGFR value of < 30 mL/min/1.73 m^2. To exclude patients with significant cardiac dysfunction, the study will exclude patients with a history of left-sided heart disease. Patients who have evidence of volume overload at baseline, defined as BNP level of > 200 pg/mL, will also be excluded.

Laboratory data will also be used to monitor fluid status after randomization. Patients that experience a BNP > 100 pg/mL that represents a doubling (or more) of BNP levels from Day 1 should be instructed to stop taking their study medication immediately and return to the clinic within 1 week (± 3 days) for an unscheduled physical examination and laboratory assessment by the investigator.

Additionally, after randomization patients will be closely monitored for rapid weight gain suggestive of fluid overload. 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 kilogram) or greater increase in weight since their Day 1 weight during the first 8 weeks will be instructed to stop taking their study medication immediately and return to the clinic for an unscheduled physical examination and laboratory assessment by the investigator.

Investigators are encouraged to start or increase 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.

Patients who experience a five-pound (2.3 kilogram) or greater increase in weight after the Week 8 study visit will be instructed to return to the clinic for an unscheduled physical examination and laboratory assessment by the investigator. Study medication should not be discontinued until the investigator has completed and documented an assessment of fluid overload.

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 should immediately assess symptoms of fluid overload and determine appropriate medical management, as necessary, including whether stopping drug administration is required. At the earliest sign of worsening or new onset peripheral edema or other signs and symptoms of acute volume overload, investigators will be expected to report if changes to a patient's diuretic regimen have been required to manage edema.

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

Nearly all instances of elevated transaminases due to bardoxolone methyl treatment are expected to be asymptomatic. Check transaminase levels (as well as TBL, GGT, alkaline phosphatase (ALP), and International Normalized Ratio (INR)) within 48 to 72 hours during an unscheduled visit if the following occurs:

- ALT or AST levels > 5X ULN

Repeat testing every 72 to 96 hours until transaminase levels are below 5X the ULN for at least one week or until the patient withdraws consent.

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

- 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/studies 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. 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. Hypomagnesaemia

In instances where a patient experiences hypomagnesaemia, 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 renal 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 associated with nephrotic syndrome. Other concurrent signs of nephrotic syndrome include serum albumin levels below 3.5 g/dL, peripheral edema, increased blood pressure, increased BNP, or other signs of fluid retention. If nephrotic syndrome is suspected, the medical monitor should be consulted to discuss appropriate measures, which may include dose adjustment, temporary study drug discontinuation, and/or administration of loop diuretics.

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 (KDIGO): ≤ 140 mm Hg systolic and ≤ 90 mm Hg diastolic for patients with UACR < 30 mg/g, and ≤ 130 mm Hg systolic and ≤ 80 mmHg diastolic for patients with UACR > 30 mg/g (KDIGO, 2012). Patients should receive the maximally tolerated labeled daily dose (MTLDD) of an ACE inhibitor and/or ARB, which is 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 (ACE inhibitor 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 ACE inhibitor 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 necessary.

9.2. Description of Study Drug

Bardoxolone methyl (RTA 402) drug product information is shown in Table 6.

Table 6: Bardoxolone Methyl Drug Product Information

Description	Bardoxolone methyl capsule (5 mg, 15 mg)
[redacted]	[redacted]
Route of Administration	Oral

9.3. Concomitant Medications

9.3.1. Excluded Medications

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

- Any other investigational drug or device as part of an interventional study;
- 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®)]. Glucocorticoid intra-articular injections, inhaled products, topical preparations, and nasal preparations are allowed. Patients with IgAN or FSGS that are receiving prednisone at doses ≤ 10 mg/day are eligible for enrollment in the IgAN or FSGS cohort, but prednisone doses must be stable for 30 days prior to Screen A visit and should be anticipated to remain the same for the remainder of the study.

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.

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 ACE inhibitors and ARBs, should be 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 and discussed with the Medical Monitor.

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. The study drug must not be used for reasons other than that described in the protocol.

9.5. Randomization

Not applicable.

9.6. Blinding

Not applicable.

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;
- Any time the investigator feels that it is clinically appropriate for patient safety.

At a minimum, unscheduled visits should include collection of AEs, clinical chemistry, hematology, concomitant medications and vital signs, as well as collection/review of weight diary. 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

Women of childbearing potential (WOCBP) are those who are not surgically sterile (no history of bilateral tubal ligation, hysterectomy, or bilateral salpingo-oophorectomy) do not have fallopian inserts with confirmed blockage, have not had reproductive potential terminated by radiation, and are not postmenopausal for at least 1 year.

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, vaginal, or transdermal) for at least 90 days prior to start of study drug administration;
- Use of an intrauterine device;
- Abstain from sexual intercourse completely. Complete abstinence from sexual 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, males who have female partners of childbearing potential must practice one of the following methods of birth control:

- Have had a vasectomy (at least 6 months earlier);

- 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 use of an intrauterine device;
- Partner use of hormonal contraceptives (oral, parenteral, vaginal or transdermal) for at least 90 days prior to start of study drug administration;
- Abstain from sexual intercourse completely. Complete abstinence from sexual 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 5. All Day 1 procedures, except AE assessments, should be completed prior to administration of first dose of study drug.

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.

9.10.2. Inclusion/Exclusion

Inclusion and exclusion criteria must be reviewed as indicated in Table 5. 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 randomizing the patient 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 5. Baseline disease characteristics will be collected as indicated in Table 5.

9.10.4. Prior and Current Concomitant Medications

The name, dose, and frequency must be recorded for all medications that 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. Concomitant medications will be reviewed as indicated in Table 5 and all changes will be recorded.

9.10.5. Medical History

A complete medical history (*e.g.*, per patient report) that includes all medical history within the past 5 years must be collected. Medical history will be recorded as indicated in Table 5.

9.10.6. Height

Height should be measured without footwear or prosthetics as indicated in Table 5.

9.10.7. Weight and Body Mass Index (BMI)

Weight must be measured as indicated in Table 5. BMI will be calculated in the eCRF each time the weight is recorded. The Sponsor will provide each patient with a scale to use at home to measure weight, and a 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 thereafter. 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.

9.10.8. Electrocardiograms (ECG)

A 12-lead ECG will be recorded as indicated in Table 5 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.

9.10.9. Echocardiogram

An echocardiogram will be recorded as indicated in Table 5 to determine patient eligibility.

9.10.10. Vital Sign Measurements

Vital sign measurements include the patient's heart 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. 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 5.

9.10.11. Physical Examination

A comprehensive physical examination must be performed by a physician, physician assistant, or registered nurse practitioner as indicated in Table 5 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 recorded as medical history. Following the examination at Screening, new or changed physical examination findings meeting the definition of an adverse event must be reported as an adverse event. If possible, the same individual should perform each physical examination on a patient during the study.

9.10.12. Pregnancy Test

WOCBP (see Section 9.8) will complete a pregnancy test as indicated in Table 5, 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. 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 one capsule from each bottle included in the study drug kit orally once a day beginning on Day 1 through the end of the study, as indicated in Table 5. Each dose of study drug should be administered at approximately the same time each day, preferably in the morning. On days when PK samples are collected, patients must not self-administer study drug. Study staff will administer study drug at the clinic following collection of the first PK sample.

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 5. The patient will be dispensed one treatment kit at Day 1, Week 2, Week 4, Week 6 (only if baseline ACR >300 mg/g) and Week 8. Dispensed treatment kits from each visit 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 5. 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 must be brought into the clinic and evaluated by the investigator as soon as possible, 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 5. 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. Kidney Biopsy

Kidney biopsies will be performed as indicated in Table 5 for patients enrolling in the IgAN or FSGS cohorts to determine patient eligibility. Detailed instructions will be provided in a separate laboratory manual provided to the investigator.

9.10.18. Fasting C-Peptide Levels

Fasting C-peptide levels will be assessed as indicated in Table 5 for patients enrolling in the T1D cohort to determine patient eligibility. Detailed instructions will be provided in a separate laboratory manual provided to the investigator.

9.10.19. Genetic Testing

Genetic testing for PKD1 mutations for patients enrolling in the ADPKD cohort will be performed as indicated in Table 5 to determine patient eligibility. Detailed instructions will be provided in a separate laboratory manual provided to the investigator

9.10.20. Clinical Chemistry

Samples will be collected for the following clinical chemistry analyses as indicated in Table 5: ferritin, creatine kinase (CK), BUN, enzymatic creatinine, eGFR, TBL, direct bilirubin, ALT, AST, ALP, sodium, potassium, calcium, phosphorus, uric acid, total protein, glucose, albumin,

lactate dehydrogenase (LDH), magnesium, chloride, bicarbonate, and GGT. Women of child-bearing potential will require a serum pregnancy test (hCG-Qual) at the Screen A visit or at any point in time if a pregnancy is suspected.

9.10.20.1. eGFR

The eGFR value will be calculated by a central laboratory and provided to the investigator by a facsimile report. 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:

$$\text{Percent Difference} = |X-Y| / ((X+Y)/2)$$

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 to calculate eGFR for each patient throughout the study, using the patient's age on the date of consent:

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

9.10.21. N-Terminal Pro-Brain Natriuretic Peptide (NT-Pro BNP) and Brain Natriuretic Peptide (BNP)

Samples will be collected for NT-Pro BNP and BNP as indicated in Table 5. As recent exercise may affect BNP and NT-Pro BNP 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.

9.10.22. Insulin-Like Growth Factor-1 (IGF-1) and Serum Ketones

Samples will be collected for IGF-1 and serum ketones as indicated in Table 5. Detailed instructions on collection, storage and shipment of the samples will be provided in a separate laboratory manual provided to the investigator.

9.10.23. Hematology

Samples will be collected for the following hematology assessments as indicated in Table 5: hematocrit, hemoglobin, hemoglobin A1c, 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).

9.10.24. Urinalysis and Microscopy

Samples will be collected for the following urinalysis and microscopy assessments as indicated in Table 5: specific gravity, ketones, pH, protein, blood, glucose, clarity, color, leukocytes, nitrite, bilirubin, and a microscopic examination (if indicated based on laboratory results).

9.10.25. Urine Collection for Albumin to Creatinine Ratio (ACR)

Albumin/creatinine ratio will be measured by first morning void spot urine collection as indicated in Table 5. 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.

[redacted]

9.10.28. Virus Serology

Blood samples will be collected for testing for hepatitis B and hepatitis C as indicated in Table 5. If the initial hepatitis C result is positive, then the patient will need to return for an unscheduled hepatitis C virus ribonucleic acid (HCV RNA) assessment to determine if the virus is present at the current time. If the results of this test are negative, the patient may continue in the Screening process.

9.10.29. Pharmacokinetic (PK) Blood Samples

Blood samples for determination of plasma bardoxolone methyl and potential metabolite concentrations will be drawn as indicated in Table 5. Patients must be instructed to not take their study drug prior to coming to the clinic for visits when PK samples will be collected. Patients will be asked by site personnel to provide the time of their last two administrations of study drug prior to the blood samples being collected. Blood sample collection instructions should be referenced in the laboratory manual. Patients must administer the study drug dose in the clinic on PK sample collection visits after the 0 hour PK blood sample is collected. Patients will have blood samples for PK analysis drawn just prior to (0 hour) and after (2 and 4 hours) dose administration.

The date and time of collection of all PK blood samples should be recorded; however, any deviations from the protocol-specified sampling times will not be considered protocol deviations.

Sample time deviations will be summarized in the study report. 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.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

Bardoxolone methyl capsules, 5 mg and 15 mg, will be used in this study.

10.2. Study Drug Packaging and Labeling

The study drug will be supplied in tamper-evident kits containing two high-density polyethylene (HDPE) bottles. Each bottle will utilize foil induction-seal liners and a child-resistant closure. Each bottle of study drug will contain 30 capsules of 5 mg or 15 mg strength bardoxolone methyl or the matching placebo capsules. 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;
- Protocol 402-C-1702;
- Caution Statement: New Drug – Limited by Federal Law to Investigational Use. Keep out of sight and reach of children;
- Control or lot number;
- Store at 20° – 25°C (68° – 77°F), short term excursions allowed to 15° – 30°C (59° – 86°F);
- Reata Pharmaceuticals, Inc., Irving, TX.

A double-panel label will be presented on the treatment kit carton containing this and other information as well.

10.3. Study Drug Storage

The stability of the drug product has been and is currently being evaluated in ongoing studies.

Investigative sites must store the investigational product in a secure location with room temperature conditions of 20° - 25°C (68° - 77°F), with short term excursions allowed to 15° – 30°C (59° – 86°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 5. Patients must be instructed to continue taking study drug once daily up through their Week 12 visit unless: (1) the patient has been otherwise instructed by the investigator or (2) the patient has been formally discontinued from study treatment.

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 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.

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 5 must be reported, regardless of their relationship to study drug or their clinical significance.

11.2.1.2. Serious Adverse Event

An 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 5 or until 30 days following administration of the final dose, 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 5 or until 30 days following administration of the final dose, 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

Moderate: Symptoms causing greater than minimal interference with usual social and functional activities

Severe: Symptoms causing inability to perform usual social and functional activities

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 30 days (+/- 3 days) following administration of the final dose of study medication, 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 5, 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 the completed SAE form to Medpace (fax numbers 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 Medpace Clinical Safety.

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 to Medpace Clinical Safety.

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 AEs which are commonly observed in this patient population will not be reported to regulatory authorities as individual expedited reports, except in unusual circumstances.

- Hypotension
- Hyperkalemia
- Fatigue
- Edema/fluid retention

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 25 patients in each cohort, the study will have approximately 80% power to detect a change from baseline in eGFR relative to zero. [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

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

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 efficacy endpoints. Baseline ACR and eGFR values will be calculated using averages of measurements collected up through Day 1, prior to first dose of study drug. The SAP will provide details of these calculations.

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 intent-to-treat (ITT) population, which includes all patients enrolled in each cohort, will be used to assess the primary efficacy endpoint for each cohort. Mixed-model repeated measures (MMRM) analyses will be used to analyze the primary efficacy endpoint for each cohort separately. Change from baseline eGFR values for all scheduled visits collected through the Week 12 visit will contribute to the primary analysis. The dependent variable will be change from baseline in eGFR. The model will include change from baseline in eGFR as the dependent variable, protocol-scheduled nominal time point as a fixed effect, patient as a random effect, and the baseline eGFR and log-transformed baseline ACR as continuous covariates. Within-patient correlations will be modeled using an unstructured covariance structure. Time ordering is a repeated measure within patients. It is assumed that errors for different patients are independent with an unstructured covariance structure. The estimation method for the model will be restricted maximum likelihood (REML). Missing data will not be imputed for the primary analysis. [redacted] Additional sensitivity analyses may be performed as appropriate.

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 Conference on Harmonisation (ICH) guideline E6(R1): 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 Food and Drug Administration (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 Good Clinical Practices and all applicable regulatory requirements, Reata may conduct a quality assurance audit of the investigator's clinical site, including CTM/IMP 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(R1) 8.2 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 International Conference on Harmonization (ICH) for Guidance for Industry on Good Clinical Practice (GCP) ICH E6(R1) [http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.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 (R1), 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 principal investigator or designee must document any protocol deviation. The IRB/EC must be notified of all protocol deviations in a timely manner by the principal investigator or designee as appropriate. Protocol deviations will be documented by the responsible monitor during monitoring visits, and those observations will be communicated to the investigator.

If there is an immediate hazard to a patient the principal investigator may deviate from the protocol without prior Sponsor and IRB/EC approval. The Sponsor and IRB/EC must be notified of the deviation.

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.

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