COVER PAGE

Official Title:	A Phase 3 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with Autosomal Dominant Polycystic Kidney Disease
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A PHASE 3 TRIAL OF THE EFFICACY AND SAFETY OF BARDOXOLONE METHYL IN PATIENTS WITH AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Version 7.0 – 25 MAY 2022

Protocol Version History

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Version 5.1 Czech Republic – 30 March 2021
Version 5.1 United Kingdom – 30 March 2021
Version 5.1 Germany – 30 March 2021
Version 5.0 – 25 February 2021
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Version 4.1 United Kingdom – 25 June 2020
Version 4.1 Germany – 25 June 2020
Version 4.0 – 25 June 2020
Version 3.1 United Kingdom – 09 January 2020
Version 3.1 Germany – 02 December 2019
Version 3.1 Czech Republic – 18 November 2019
Version 3.0 – 16 July 2019
Version 2.0 – 04 March 2019
Version 1.0 – 12 December 2018

SPONSOR APPROVAL AND SIGNATURE PAGE

{See Appended Electronic Signature Page}

[redacted] M.D.
[redacted]

Date

{See Appended Electronic Signature Page}

[redacted]

Date

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Date

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Date

INVESTIGATOR'S AGREEMENT

I have read the 402-C-1808 clinical study protocol and agree to conduct the study as outlined. I have received and read the Investigator's Brochure for bardoxolone methyl. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Medical and Scientific Leader	[redacted] MD. [redacted] [redacted] Reata Pharmaceuticals, Inc.	[redacted] [redacted] Office: [redacted]
Clinical Operations Personnel	[redacted] [redacted] [redacted] Reata Pharmaceuticals, Inc.	[redacted] [redacted] Office: [redacted]
Medical Monitor	Medical Monitor Team Reata Pharmaceuticals, Inc.	[redacted] [redacted] Office: [redacted] Email: [redacted]
SAE Reporting	[redacted] [redacted] [redacted] E-mail: [redacted]	

2. SYNOPSIS

Name of Sponsor/Company:
Reata Pharmaceuticals, Inc.

Name of Investigational Product:
Bardoxolone methyl

Title of Study:
A Phase 3 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with Autosomal Dominant Polycystic Kidney Disease

Study center(s): Up to 200 study centers

Studied period: ~ 6 years Estimated date first patient enrolled: May 2019 Estimated date last patient completed: November 2025 The end of the study is defined as the last visit of the last patient.	**Phase of development:** 3

Objectives:
For patients with autosomal dominant polycystic kidney disease (ADPKD) enrolled in this study, the objectives to assess bardoxolone methyl relative to placebo are as follows:

Primary:

- To assess the off-treatment change from baseline in estimated glomerular filtration rate (eGFR) at Week 108.
- To assess safety and tolerability.

Secondary:

- To assess the change from baseline in eGFR at Week 100.
- [redacted]
- To assess the off-treatment change from baseline in eGFR at Week 112.
- [redacted]
- [redacted]
- [redacted]
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Methodology:

This international, multi-center, randomized, double-blind, placebo-controlled phase 3 trial will study the safety, tolerability, and efficacy of bardoxolone methyl in qualified patients with ADPKD. Approximately 850 patients will be enrolled.

Patients will be randomized 1:1 to either bardoxolone methyl or placebo. Randomization will be stratified by eligibility eGFR category (30 to <60; ≥60 to 90), concomitant tolvaptan use (yes, no), and screening albumin to creatinine ratio (ACR; ≤300 mg/g, >300 mg/g). Patients randomized to placebo will remain on placebo throughout the study, undergoing sham titration. Patients with eGFR 60 to 90 mL/min/1.73 m^2 at screening should not comprise more than approximately 40% of enrolled patients.

The maximum bardoxolone methyl dose will be determined by baseline proteinuria status. 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 receiving bardoxolone methyl will start with once-daily dosing at 5 mg and will dose-escalate to 10 mg at Week 2, to 20 mg at Week 4, and then to 30 mg at Week 6 (only if 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.

All patients in the study will follow the same visit and assessment schedule. Following randomization on Day 1, patients will be assessed during treatment in-person at Week 1, 2, 4, 6, 8, 12, 24, 36, 48, 52, 64, 76, 88, and 100 and by telephone contact on Day 3, 10, 21, 31, 38, and 45. Patients will continue study drug treatment through Week 100. Patients will also be assessed during follow-up in-person at Weeks 103, 104, 108, and 112.

Efficacy endpoints will be analyzed after all enrolled patients have completed the study and the database has been locked. All enrolled patients are expected to remain on their blinded treatment assignment through Week 100 and to complete all scheduled assessments through Week 112.

The conduct of the study, according to protocol specifications, was impacted by the COVID-19 (Coronavirus Disease 2019) pandemic. As a result, and as of Version 4 of the protocol, modifications intended to address access to and administration of study drug, and adherence to protocol-specified visits and laboratory assessments were implemented. These modifications are described in Appendix 1 (COVID-19 Mitigations), Appendix 2 (Use of Home Healthcare) and throughout the protocol.

Number of patients (planned):

Approximately 850 patients will be enrolled.

Diagnosis and main criteria for inclusion:

1. Male and female patients 12 ≤ age ≤ 70 upon study consent;
2. Diagnosis of ADPKD:
    a. For adult (18 ≤ age ≤ 70) diagnosis of ADPKD by modified Pei-Ravine criteria:
        i. at least 3 cysts per kidney by sonography or at least 5 cysts by CT or MRI with family history of ADPKD; or
        ii. at least 10 cysts per kidney by any radiologic method and exclusion of other cystic kidney diseases if without family history;
    b. For adolescent (12 ≤ age < 18) diagnosis of ADPKD by:
        i. the presence of family history and/or genetic diagnosis and the presence of at least 1 cyst of 0.5 cm on ultrasound or MRI; or
        ii. patients without a family history or genetic diagnosis must have at least 10 bilateral renal cysts in total, and exclusion of other cystic kidney diseases.
3. eGFR must:
    a. Have a percent difference ≤ 25% at screening (the values at Screen A and Screen B) and;
    b. Have an average (the values at Screen A and Screen B) ≥ 30 to ≤ 90 mL/min/1.73 m^2 for patients 12 to 55 years or ≥ 30 to ≤ 44 mL/min/1.73 m^2 for patients 56 to 70 years and;
    c. Support ADPKD disease progression (i.e., average yearly eGFR decline of ≥ 2.0 mL/min/1.73 m^2 for the past two years) for patients with either screening eGFR≥ 60 to ≤ 90 mL/min/1.73 m^2 or age 56 to 70 years (See Protocol Section 9.10.2)
4. ACR ≤ 2500 mg/g at Screen B visit;
5. Systolic blood pressure ≤ 140 mmHg and diastolic blood pressure ≤ 90 mmHg at Screen A or Screen B visit after a period of rest. Patients receiving an angiotensin-converting enzyme (ACE) inhibitor and/or an angiotensin II receptor blocker (ARB)* must be on a stable dose for at least 6 weeks prior to the Screen A visit; *see Protocol Section 9.1.7
6. 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), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ the upper limit of normal (ULN);
7. Able to swallow capsules;

8. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures;
9. Evidence of a personally signed and dated informed consent/assent document indicating that the patient has been informed of all pertinent aspects of the study prior to initiation of any protocol-mandated procedures.
10. Patients receiving an SGLT2 inhibitor must be on a stable dose for at least 4 weeks prior to the Screen A visit

Major exclusion criteria:

1. Prior exposure to bardoxolone methyl;
2. Use of tolvaptan within 2 months prior to Screen A. Initiation of concomitant tolvaptan use during the study is not permitted;
3. History of administration of polycystic kidney disease-modifying agents (somatostatin analogues) within 2 months prior to the Screen A visit;
4. B-type natriuretic peptide (BNP) level > 200 pg/mL at Screen A visit;
5. Uncontrolled diabetes (HbA1c > 11.0%) at Screen A visit;
6. Serum albumin < 3 g/dL at Screen A visit;
7. History of intracranial aneurysms;
8. Kidney or any other solid organ transplant recipient or a planned transplant during the study;
9. Acute dialysis or acute kidney injury within 12 weeks 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 III or IV;
    h. History of untreated atrial fibrillation;
    i. History of unstable arrhythmias;
11. Systolic BP < 90 mm Hg at Screen A visit after a period of rest;
12. BMI < 18.5 kg/m^2 at the Screen A visit;
13. History of malignancy within 5 years prior to Screen A visit, with the exception of localized skin or cervical carcinomas;
14. Systemic immunosuppression for more than 2 weeks, cumulatively, within the 12 weeks prior to randomization or anticipated need for immunosuppression during the study;
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;
22. Coronavirus disease 2019 (COVID-19) pneumonia, related acute kidney injury, or related hospitalization within 6 months prior to Day 1.

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 or placebo will be administered through Week 100.

Reference therapy, dosage and mode of administration:

Placebo will be administered orally through Week 100.

Criteria for evaluation:

Efficacy: Change from baseline in eGFR; [redacted]

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

Statistical methods:

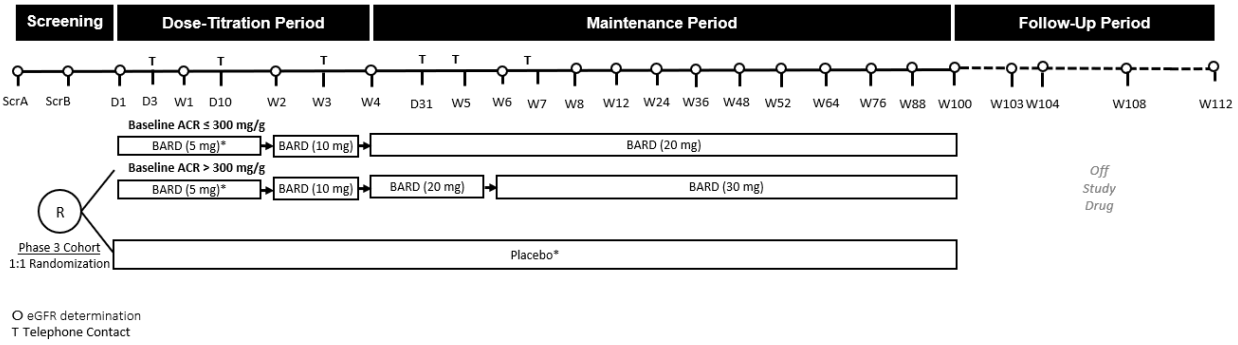
Sample size:

With 850 patients enrolled, the study will have approximately 80% power to detect a difference between the two treatment groups in change from baseline eGFR of 2.3 mL/min/1.73 m^2. The power calculation was based on a 2-sample t-test as an estimate for the planned ANCOVA analysis and assumes the following:

- Overall two-sided Type I error rate of 0.05;
- Standard deviation of change from baseline in eGFR of 12 mL/min/1.73 m^2;
- Analyses are based on the intent-to-treat (ITT) population;
- Missing data will be imputed using multiple imputation.

ANCOVA analysis expected to have approximately the same power as the t-test used for study planning. The method for maintaining strict control of the Type I error for the trial will be described in the statistical analysis plan (SAP). Appropriate sensitivity analyses of the primary analysis will be specified in the SAP.

Schema for Study of Bardoxolone Methyl in Patients with ADPKD



3. TABLE OF CONTENTS AND LIST OF TABLES

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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
ABPM	Ambulatory Blood Pressure Monitoring
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]
CGMP	Current Good Manufacturing Practices
CK	Creatine kinase
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Coronavirus Disease 2019
CrCl	Creatinine clearance
CV	Cardiovascular
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	Electronic case report form
ECG	Electrocardiogram
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ERA	Endothelin receptor antagonist

Abbreviation or Specialist Term	Explanation
ESKD	End stage kidney disease
FDA	Food and Drug Administration (US)
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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Response System
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
MRI	Magnetic resonance imaging
MTLDD	Maximally tolerated labeled daily dose
Nrf2	Nuclear factor (erythroid-derived 2)-related factor 2
NT-Pro BNP	N-Terminal Pro-Brain Natriuretic Peptide
PBO	Placebo
[redacted]	[redacted]
[redacted]	[redacted]
PH	Pulmonary hypertension
PK	Pharmacokinetic
PT	Prothrombin Time
QTc	Corrected QT interval

Abbreviation or Specialist Term	Explanation
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SGLT2i	Sodium-glucose co-transporter 2 inhibitors
T2D	Type 2 diabetes
TBL	Total bilirubin
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WOCBP	Women of childbearing potential

5. INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a multi-organ disorder that results in clusters of fluid-filled cysts in the kidneys and other organs leading to progressive enlargement and loss of organ function. ADPKD is a genetic disorder caused by mutations in the PKD1 and PKD2 genes, which encode the proteins polycystin-1 and -2, respectively. The PKD1 and PKD2 mutations disrupt the function of these proteins within the cilia, forming fluid-filled cysts that progressively increase in size, leading to gross enlargement of the kidneys and distortion of the renal architecture. The disease is the leading inheritable cause of kidney failure; the number of diagnosed patients in the United States is estimated to be between 100,000 and 200,000.

Although cystogenesis is initiated by mutations in polycystin and other genes, inflammation plays a primary role in cyst growth and is associated with disease progression in ADPKD (Karihaloo, 2015). Renal cyst formation and growth in ADPKD triggers 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 kidney function. Thus, the pathogenic role of inflammatory processes in ADPKD disease progression and declining renal function is similar to that of other forms of chronic kidney disease (CKD).

Bardoxolone methyl activates molecular pathways that promote the resolution of inflammation by restoring mitochondrial function, reducing oxidative stress, and inhibiting reactive oxygen species (ROS)-mediated pro-inflammatory signaling. Bardoxolone methyl binds to Kelch-like ECH-associated protein 1 (Keap1) and activates nuclear factor, erythroid 2-like 2 (Nrf2), a transcription factor that increases cellular antioxidant and detoxification enzymes and promotes normal mitochondrial function by making reducing equivalents available for adenosine triphosphate (ATP) production. These anti-inflammatory and tissue-protective effects of bardoxolone methyl suppress multiple cellular processes that conspire to promote glomerular filtration rate (GFR) loss in ADPKD. *In vitro* studies in renal cyst cell lines have shown that bardoxolone methyl significantly suppresses markers of inflammation (e.g., MCP-1) which are associated with cyst formation and growth. Bardoxolone methyl also reverses endothelial dysfunction and pathogenic mesangial cell contraction, resulting in increased glomerular filtration surface area (K_f) and GFR. Additionally, bardoxolone methyl inhibits activation of inflammatory and pro-fibrotic pathways that lead to structural remodeling and glomerulosclerosis. As a result, bardoxolone methyl has been shown to reduce inflammation, improve renal function, and prevent injury, remodeling, and fibrosis in many animal models of renal injury and disease.

Bardoxolone methyl has consistently improved parameters of renal function in multiple clinical studies in patients with CKD, cancer, or 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 estimated glomerular filtration rate (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 and dynamic inflammation-mediated processes such as 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 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 end stage kidney disease (ESKD). 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.

In summary, bardoxolone methyl has the potential to inhibit inflammation-mediated pathways that contribute to disease progression and GFR loss in ADPKD. Despite available therapies, patients with ADPKD have progressively declining kidney function, with average estimated glomerular filtration rate (eGFR) declines of 2.8 to 3.8 mL/min/1.73m^2 per year (Torres, 2012; Boertien, 2013; Schrier, 2014; Torres, 2017). Thus, the potential impact of a sustained eGFR increase with bardoxolone methyl treatment is profound and could provide a multi-year delay in disease progression to ESKD in patients with ADPKD.

Although tolvaptan is approved for the treatment of ADPKD, there remains a significant need for additional treatment options for these patients, who still have progressive loss of kidney function despite approved therapies. A placebo-controlled trial with bardoxolone methyl provides the best opportunity to determine the benefit-risk profile for bardoxolone methyl in ADPKD patients. The use of a placebo comparator in the 402-C-1808 trial is justified because the known safety profile of tolvaptan, together with the known pharmacologic effects of bardoxolone methyl, would complicate regulatory agency recommendations for safety monitoring and medical management of patients in a double-blind trial. Furthermore, it may interfere with the efficacy assessment in ADPKD patients. For these reasons, Reata believes the use of a placebo comparator is justified.

Treatment of patients with ADPKD disease progression is a significant unmet need. Adolescent patients with an average yearly eGFR decline of $\geq$ 2.0 mL/min/1.73 m^2 for two years prior to study entry are at risk of developing ESKD earlier than other adolescent ADPKD patients. At present for adolescent ADPKD patients, there is no drug approved for CKD treatment. The current study will evaluate the efficacy and safety of bardoxolone methyl for treatment of CKD due to ADPKD.

The study participation burden for patients including multiple study visits, laboratory tests and other required assessments may outweigh the risk of potential anticipated benefit of the study results. The Sponsor will undertake all reasonable measures to minimize the study burden and risk to the patients. This study will provide additional efficacy and safety information on the risk: benefit profile of bardoxolone methyl.

5.1. Clinical Experience with Bardoxolone Methyl

Overall, bardoxolone methyl has been tested in multiple studies enrolling over 3,000 patients, and over 2,500 individuals have been exposed to bardoxolone methyl.

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 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 2,700 patients with type 2 diabetes and CKD, bardoxolone methyl has been shown to consistently produce clinically and statistically significant improvements in eGFR that are durable for at least one year in treated patients.

Study 402-C-0804 ("BEAM") was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, multi-dose, Phase 2b study designed to assess the efficacy and safety of 3 doses (25, 75, and 150 mg) of the crystalline formulation of bardoxolone methyl in patients with Stage 3b-4 CKD (eGFR 20-45 mL/min/1.73 m^2) and type 2 diabetes. 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 kidney disease (ESKD; 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 Kirin Co., Ltd, demonstrated that bardoxolone methyl treatment resulted in a significant improvement in measured GFR, as assessed by inulin clearance, 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.

Bardoxolone methyl was also shown to significantly increase eGFR in patients with CKD due to Alport syndrome after 12 weeks of treatment. The increases in eGFR from baseline at Week 12 were shown to be sustained through 48 weeks of treatment (10.4 mL/min/1.73 m^2; n=25; $p<0.0001$) and partially retained four weeks after withdrawal of study drug (4.1 mL/min/1.73 m^2; $p<0.001$). The clinical activity of bardoxolone methyl in Alport syndrome and diabetic nephropathy, two diseases with distinct etiologies (type IV collagen defects versus hyperglycemia, respectively), suggests that the anti-inflammatory and anti-fibrotic effects of bardoxolone methyl target the common final pathways contributing to GFR loss in multiple forms of chronic kidney diseases.

Most recently, bardoxolone methyl was studied in a Phase 2 trial (study 402-C-1702, PHOENIX, NCT03366337) in patients with four rare forms of CKD: genetically-confirmed autosomal dominant polycystic kidney disease (ADPKD), biopsy-confirmed IgA nephropathy (IgAN), diabetic nephropathy secondary to type 1 diabetes (T1D), or biopsy-confirmed focal segmental glomerulosclerosis (FSGS). In the cohort of patients with ADPKD with PKD1 mutations, treatment with bardoxolone methyl significantly increased eGFR after treatment with 12 weeks (mean ± SE: 9.3 ± 1.4 mL/min/1.73 m^2; n=31; $p<0.0001$). The improvements were consistent, and 27 of the 28 (96%) patients with data at Week 12 had improvements from baseline in eGFR. The increases were observed across multiple subgroups including age, gender, baseline eGFR, and baseline albumin to creatinine ratio (ACR). Historical eGFR data for 29 of the 31 patients showed that these patients' kidney function was declining at an average annual rate of 4.8 mL/min/1.73 m^2 prior to study entry. Therefore, the improvements in eGFR after 12 weeks of treatment with bardoxolone methyl represents a recovery of approximately two years of average eGFR loss in ADPKD patients. Thus, the magnitude and durability of eGFR increases with bardoxolone methyl could provide a meaningful therapeutic benefit, even over the sole available therapy (tolvaptan) in ADPKD.

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

Study	Phase/ Country	Study Population	# of Patients	Treatment Duration	ΔeGFR (mL/min/1.73m^2)[a]
CKD Studies					
402-C-0801 (Stratum 1) (open label)	2a/ US	Age ≥ 18, Diabetic nephropathy	60	28 days	6.7 (p<0.001)
402-C-0801 (Stratum 2) (open label)	2b/ US	Age ≥ 18, Diabetic nephropathy	20	56 days	7.2 (p<0.001) CrCl also sig. increased
402-C-0804 (BEAM)	2/ US	Age ≥ 18, T2D and CKD	227	52 weeks	8.6 at WK52 (p<0.001 vs PBO)
402-C-0902	2/ US	Age ≥ 18, T2D and CKD	131	85 days	6.5 (p<0.001)
402-C-0903 (BEACON)	3/ Global	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	Age ≥ 18, T2D and Stage 3b and Stage 4 CKD	24	56 days	9.0 (p<0.05)
RTA402-005 (TSUBAKI)	2/ Japan	Age ≥ 20, T2D and Stage 3 and 4 CKD	120	16 weeks	6.6 (inulin GFR) (p=0.008 vs PBO)
402-C-1603	2/US	Age 12 to 65, Alport Syndrome	30	48 weeks	10.4 (p<0.0001)
402-C-1603 (Year 1)	3/Global	Age 12 to 70, Alport Syndrome	157	48 weeks	9.5 (p<0.001 vs PBO)
402-C-1702	2/US	Age 18 to 70, ADPKD	31	12 weeks	9.3 (p<0.0001)
402-C-1702	2/US	Age 18 to 70, IgA Nephropathy	26	12 weeks	8.0 (p<0.0001)
402-C-1702	2/US	Age 18 to 70, T1D CKD	28	12 weeks	5.5 (p=0.025)
402-C-1702	2/US	FSGS	18	12 weeks	7.8 (p=0.003)
Non-CKD Studies					
402-C-0501	1/ US	Age ≥ 18, Advanced Solid Tumors or Lymphoid Malignancies	47	Median: 56 days	18.2 (p<0.0001)
402-C-0702	1/2/ US	Pancreatic Cancer	34	Median: 56 days	32.2 (p=0.001)
402-C-1302 (LARIAT)	2/ US	Age 18 to 75 PH (Baseline eGFR 82 mL/min/1.73 m^2)	54[b]	16 weeks	14.7 (p<0.001 vs PBO)

[a] Unless noted, 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.

[b] Number of patients enrolled in 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 patients, 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, and hepatotoxicity has not been observed. 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 upper limit normal (ULN). The elevations resolved to levels less than the ULN in most patients with elevations, within two weeks after peak values while patients continued taking study drug. Patients who experienced elevations to greater than 3X the ULN sometimes required additional time to resolve. While some patients have had elevations to

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

Bardoxolone methyl regulates gamma-glutamyl transpeptidase GGT, a known Nrf2 target gene protein. In clinical studies, low level GGT elevations during treatment were common, mild, and typically lasted longer than alanine aminotransferase (ALT)/ aspartate aminotransferase (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 patients 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 commonly 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 CKD 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.

5.1.2.7. Impact on Adolescent Growth (Weight and Height)

Impacts on weight and height gain were observed in bardoxolone methyl-treated adolescent patients (ages 12-17 years) with Alport syndrome (study 402-C-1603 CARDINAL) when compared to placebo-treated adolescent patients. In this study, a total of 23 adolescents were enrolled, where 11 and 12 were randomized to bardoxolone methyl and placebo, respectively.

In bardoxolone methyl treated adolescents, both weight and height at baseline were relatively higher than placebo treated adolescents. Bardoxolone methyl treated patients had a mean baseline weight of 65.50 kg (SD 10.193, median 63.90 kg, min/max 52.5/81.3 kg), while placebo

treated adolescents had a mean baseline weight of 57.79 kg (SD 16.020, median 59.80 kg, min/max 29.5/76.3 kg). A change from baseline using the last on treatment value available for weight showed a mean weight decrease of -1.41 kg (SD 5.260, median -2.30 kg, min/max -10.9 to 6.8 kg) for bardoxolone methyl treated adolescents and a mean weight increase of +2.26 kg (SD 4.153, median +2.25 kg, min/max -5.7 to +8.2 kg) for placebo treated adolescents.

Bardoxolone methyl treated adolescents at baseline had a mean height of 171.7 cm (SD 5.90, median 172.0 cm, min/max 165/183 cm), while placebo treated adolescents had a mean height of 166.3 cm (SD 14.94, median 169.5 cm, min/max 136/186 cm). A change from baseline using the last on treatment value available showed a mean height increase of +1.1 cm (SD 1.13, median +1.0 cm, min/max 0 to 3 cm) for bardoxolone methyl treated adolescents, compared with a mean height increase of +2.4cm (SD 3.65, median 0.6 cm, min/max -1 to +11cm) for placebo treated adolescents.

Bardoxolone methyl treated adolescents at baseline had a mean BMI of 22.1 kg/m^2 (SD 2.11, median 22.3 kg/m^2, min/max 19/25 kg/m^2), while placebo treated adolescents at baseline had a mean BMI of 20.5 kg/m^2 (SD 3.63, median 20.3 kg/m^2, min/max 16/26 kg/m^2). Overall, in bardoxolone methyl treated adolescents, BMI changes from baseline to last value on treatment showed a mean decrease of -0.5 kg/m^2 (SD 1.40, median -0.8 kg/m^2, min/max -3/+2 kg/m^2), compared with a mean BMI increase in placebo treated adolescents of 0.3 kg/m^2 (SD 1.15, median 0.3 kg/m^2, min/max -2/+2 kg/m^2).

In Study 402-C-1603 phase 3, the number of adolescent subjects was relatively small; therefore, a firm conclusion cannot be derived. Overall, no other concerning differences in the safety profile were identified in patients 12 to < 18 years of age compared to adult patients randomized to receive bardoxolone methyl (total: n=77; adults: n=66) or to receive placebo (total: n=80; adults: 68).

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

The objectives are as follows:

6.1.1. Primary Objective

- To assess the off-treatment change from baseline in estimated glomerular filtration rate (eGFR) at Week 108.
- To assess safety and tolerability.

6.1.2. Secondary Objective

- To assess the change from baseline in eGFR at Week 100.

[redacted]

- [redacted]
- To assess the off-treatment change from baseline in eGFR at Week 112.
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6.2. Endpoints

6.2.1. Primary Efficacy Endpoint

- Off-treatment change from baseline in eGFR at Week 108.

6.2.2. Secondary Efficacy Endpoint

- Change from baseline in eGFR at Week 100.

[redacted]

- [redacted]
- The off-treatment change from baseline in eGFR at Week 112.
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6.2.4. 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, pediatric growth (height and weight), and sexual maturity using Tanner staging.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This international, multi-center, randomized, double-blind, placebo-controlled phase 3 trial will study the safety, tolerability, and efficacy of bardoxolone methyl in qualified patients with ADPKD. Approximately 850 patients will be enrolled.

Patients will be randomized 1:1 to either bardoxolone methyl or placebo. Randomization will be stratified by eligibility eGFR category (30 to <60; ≥60 to 90), concomitant tolvaptan use (yes, no), and screening ACR (≤300 mg/g, >300 mg/g). Patients randomized to placebo will remain on placebo throughout the study, undergoing sham titration. Patients with eGFR 60 to 90 mL/min/1.73 m^2 at screening should not comprise more than approximately 40% of enrolled patients.

The maximum bardoxolone methyl dose will be determined by baseline proteinuria status. 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 receiving bardoxolone methyl will start with once-daily dosing at 5 mg and will dose-escalate to 10 mg at Week 2, to 20 mg at Week 4, and then to 30 mg at Week 6 (only if 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.

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, 12, 24, 36, 48, 52, 64, 76, 88, and 100 and by telephone contact on Days 3, 10, 21, 31, 38, and 45. Patients will continue study drug treatment through Week 100. Patients will also be scheduled to be assessed at an in-person follow-up visit at Weeks 103, 104, 108, and 112 after the end of treatment, respectively.

Efficacy endpoints will be analyzed after all enrolled patients have completed the study and the database has been locked. All enrolled patients are expected to remain on their blinded treatment assignment through Week 100, and to complete all scheduled assessments through Week 112.

The conduct of the study, according to protocol specifications, was impacted by the Coronavirus Disease 2019 (COVID-19) pandemic. As a result, and as of Version 4 of the Protocol, modifications intended to address access to and administration of study drug, and adherence to protocol-specified visits and laboratory assessments were implemented. These modifications are described in Appendix 1 (COVID-19 Mitigations), Appendix 2 (Use of Home Healthcare) and throughout the protocol.

7.2. Number of Patients

Approximately 850 patients will be enrolled.

7.3. Treatment Assignment and Dosing Rationale

Patients will be randomized 1:1 to either bardoxolone methyl or placebo. Randomization will be performed using an interactive web response system (IWRS). Patients randomized to placebo will remain on placebo throughout the study but will follow sham titration to maintain the blind.

The use of a placebo comparator is justified because the known safety profile of tolvaptan (approved for the treatment of ADPKD in adults with evidence of rapidly progressing disease) pertaining liver toxicity would interfere with known pharmacologic effects of bardoxolone methyl on aminotransferases increase without liver toxicity, and complicate safety monitoring and medical management of patients in a double-blind trial. A placebo-controlled trial with bardoxolone methyl provides the best opportunity to determine the benefit-risk profile for bardoxolone methyl in ADPKD patients. 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 higher bardoxolone methyl doses may be required to have an optimal effect on eGFR following drug withdrawal in patients with macroalbuminuria. Specifically, eGFR improvements in patients with normo- or micro-albuminuria were observed with a 20 mg bardoxolone methyl dose and the effects were retained following a 1-month withdrawal. 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 $\leq$ 300 mg/g and a maximum dose of 30 mg for patients with ACR > 300 mg/g, as described below. The same dose titration regimen was used in a Phase 2 trial in adult ADPKD patients (study 402-C-1702). 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. Adolescent Dosing Rationale

Adolescents (12 $\leq$ age < 18) will receive the same dosing regimen as adults. The maximum bardoxolone methyl dose will be determined by baseline proteinuria status. Similar to the adult population, a 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.

Although no adolescent (12 $\leq$ age < 18) patients with CKD due to ADPKD have been exposed to bardoxolone methyl, in Study 402-C-1603 (CARDINAL) phase 2/3 studies and an open-label extended access study in Alport syndrome (Study 402-C-1803, EAGLE), a total of 21 adolescent patients received bardoxolone methyl at a maximum dose of 20 mg for patients with baseline ACR $\leq$ 300 mg/g and a maximum dose of 30 mg for patients with baseline ACR > 300 mg/g. In CARDINAL phase 2/3 studies, the dose titration for adolescent patients was similar to adults, differing only during the first week, where adolescents administered study drug (at the 5 mg dose) every other day, while adults (also at the 5 mg dose) administered study drug daily. An overall safety/tolerability evaluation of adolescent patients from CARDINAL phase 2 (open-label- n=2) and Phase 3 (double-blind placebo-controlled – n=11) showed the dosing

regimen was well tolerated and the adverse event profile in adolescent patients was similar to the adverse events profile observed in the adult patients.

Additionally, a population pharmacokinetic (popPK) analysis was conducted for bardoxolone methyl using rich and sparse PK data from 8 clinical studies in healthy subjects and patients with Alport syndrome, PAH, T2DM CKD, ADPKD, and other rare CKDs (Study REAT-BARD-PMX-1532). The effects of intrinsic factors on bardoxolone methyl PK were evaluated in the popPK analysis and showed that no dose adjustments based on sex, age, body weight, race, or renal function are needed. To further support dosing recommendations based on age, simulations using the popPK model were performed to assess the potential effects of age on bardoxolone methyl steady-state exposures. Simulations were conducted following 20 mg QD and used individual posthoc PK parameter estimates for all patients and subjects in the popPK analysis dataset. Model predictions demonstrate a lack of a clinically meaningful difference in exposures between patients and subjects <18 years of age and patients and subjects ≥18 years of age (ratio of median exposures: 0.93 to 1.11). In addition, the systemic clearance of bardoxolone methyl was not affected by disease state in the popPK analysis. Therefore, there are no differences in systemic exposure (AUC) expected between patients with ADPKD and patients with Alport syndrome. The popPK model predicted mean steady-state AUC for patients receiving 30 mg QD (n=16) in Study 402-C-1702 (rare CKDs, including ADPKD) is 222 ng*hr/ml (SD = 134 ng*hr/ml), and is similar to the popPK model predicted mean steady-state AUCs of 263 ng*hr/ml (SD = 135 ng*hr/ml) and 223 ng*hr/ml (SD = 155 ng*hr/ml) in Alport syndrome patients receiving 30 mg QD in the phase 2 (n=9) and phase 3 (n-24) portions of Study 402-C-1603), respectively.

In summary, there were no differences in adverse event profiles in adolescent and adult patients who received bardoxolone methyl in CARDINAL phase 2/3 studies, and a popPK analysis suggested there are no expected differences in systemic exposure (AUC) between ADPKD and Alport syndrome patients and no age dependent requirements for dose adjustments. Therefore, the same dosing regimen is proposed both for adolescent and adult ADPKD patients.

7.3.2. Dose Escalation Plan

Both adult and adolescent patients randomized to placebo will remain on placebo throughout the study, undergoing sham titration. Both adult and adolescent patients receiving bardoxolone methyl will start with once-daily dosing at 5 mg and will dose-escalate to 10 mg at Week 2, to 20 mg at Week 4, and then to 30 mg at Week 6 (only if baseline ACR > 300 mg/g) unless contraindicated clinically and approved by the Medical Monitor.

7.3.3. Dose De-Escalation and Re-Escalation

For detailed instructions on dose management, refer to Section 9.11.

7.3.4. Dose Interruption and Re-Challenge/Re-Initiation

For detailed instructions on dose management, refer to Section 9.11.

7.4. Criteria for Study Termination

Although the Sponsor intends to complete the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons, or if required by

regulatory agencies. If the Sponsor discontinues the study, all study drug will be discontinued, and the investigator will be responsible for securing any alternative therapy to be administered, as appropriate.

7.5. Schedule of Assessments

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

Table 4: Schedule of Assessments

	Screening Period		Treatment Period											
	Screen A[a]	Screen B[b]	Day 1[c]	Wk 1 (Phone)	Wk 1	Wk 2 (Phone)	Wk 2	Wk 3 (Phone)	Wk 4	Wk 4 (Phone)	Wk 5 (Phone)	Wk 6	Wk 7 (Phone)	Week 8
	Up to Day -90	Up to Day -30	Day 1	Day 3 ±2 Days	Day 7 ±3 Days	Day 10 ±2 Days	Day 14 ±3 Days	Day 21 ±2 Days	Day 28 ±3 Days	Day 31 ±2 Days	Day 38 ±2 Days	Day 42 ±3 Days	Day 45 ±2 Days	Day 56 ±3 Days
Informed Consent/Assent	X													
Inclusion/Exclusion X			X[d]											
Demographics & Baseline Disease Characteristics	X													
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History	X													
Height[e]	X	X	X		X		X		X			X		X
Weight in Clinic	X		X		X		X		X			X		X
Weight at Home			----------X----------											
Dispense Weight & Study Drug Diary			X				X		X			X		X
Collect/Review Weight & Study Drug Diary				X	X	X	X	X	X	X	X	X	X	X
ECG	X													
Echocardiogram[f]	X													
Vital Sign Measurements	X	X[g]	X		X		X		X			X		X
Comprehensive Physical Exam	X		X											
Targeted Physical Exam					X		X		X			X		X
Pregnancy Test for WOCBP[h]	X	X	X						X					X
Study Drug Administration			----------X----------											

Dispense Study Drug			X				X		X			X		X
Collect Study Drug							X		X			X		X
Telephone Contact				X		X		X		X	X		X	
Adverse Event Collection			X[i]	X	X	X	X	X	X	X	X	X	X	X
Kidney Ultrasound[j]	X													
Clinical Chemistry (incl. eGFR)[k]	X	X	X		X		X		X			X		X
BNP and NT-proBNP	X		X		X		X		X			X		X
Hemoglobin A1c	X													
Hematology	X		X				X		X			X		X
Coagulation			X				X		X			X		X
Basic Lipid Panel			X											
Urinalysis and Microscopy	X		X				X		X			X		X
Urine Collection for ACR[l]		X							X					X
[redacted]														
Virus Serology	X													
PK Samples[n]														
SARS-CoV-2 Antibody Test			X											
Ambulatory Blood Pressure Monitoring[o]	X[p]													
Tanner Staging[q]			X											

	Treatment Period								
	Wk 12	Wk 24	Wk 36	Wk 48	Wk 52 (B)	Wk 64	Wk 76	Wk 88	Wk 100 or End of Treatment
	Day 84 ±3 Days	Day 168 ±3 Days	Day 252 ±3 Days	Day 336 ±3 Days	Day 364 ±3 Days	Day 448 ±5 Days	Day 532 ±5 Days	Day 616 ±5 Days	Day 700 -5 Days (+0 Days)
Informed Consent/Assent									
Inclusion/Exclusion									
Demographics & Baseline Disease Characteristics									
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X
Medical History									
Height[e]	X	X	X	X	X	X	X	X	X
Weight in Clinic	X	X	X	X	X	X	X	X	X
Weight at Home	----------X----------								
Dispense Weight & Study Drug Diary	X	X	X	X	X	X	X	X	
Collect/Review Weight & Study Drug Diary	X	X	X	X	X	X	X	X	X
ECG				X	X				X
Echocardiogram[f]									
Vital Sign Measurements	X	X	X	X	X	X	X	X	X
Comprehensive Physical Exam					X				X
Targeted Physical Exam	X	X	X	X		X	X	X	
Pregnancy Test for WOCBP[h]	X	X	X	X	X	X	X	X	X
Study Drug Administration	----------X----------								
Dispense Study Drug	X	X	X	X	X	X	X	X	
Collect Study Drug	X	X	X	X	X	X	X	X	X
Telephone Contact									
Adverse Event Collection	X	X	X	X	X	X	X	X	X
Kidney Ultrasound[j]									
Clinical Chemistry (incl. eGFR)[k]	X	X	X	X	X	X	X	X	X
BNP and NT-proBNP	X	X	X	X	X	X	X	X	X
Hemoglobin A1c	X			X					X
Hematology	X	X	X	X	X	X	X	X	X
Coagulation	X	X	X	X	X	X	X	X	X
Basic Lipid Panel					X				X
Urinalysis and Microscopy	X	X	X	X	X	X	X	X	X
Urine Collection for ACR[l]	X	X	X	X	X	X	X	X	X
[redacted]									
Virus Serology									
PK Samples[n]	X								X
SARS-CoV-2 Antibody Test					X				
Ambulatory Blood Pressure Monitoring [o]	X			X				X[r]	
Tanner Staging [q]					X				

	Off-Treatment Period[s]						
	Wk 103	Wk 104 (A)	Wk 104 (B)	Wk 108 (A)	Wk 108 (B)	Wk 112 (A)	Wk 112 (B)
Off-Treatment: Patients who continued study drug through Wk 100 (visits based on date of last dose)	Day 21 – 25 after last dose	Day 28 – 35 after last dose	Day 29 – 36 after last dose	Day 56 – 63 after last dose	Day 57 – 64 after last dose	Day 84 – 91 after last dose	Day 85 – 92 after last dose
Follow-Up: Patients who discontinued study drug prior to Wk 100 (visits based on Day 1 date)	Day 721 - 725	Day 728 – 735	Day 729 – 736	Day 756 – 763	Day 757 – 764	Day 784 – 791	Day 785 – 792
Informed Consent/Assent							
Inclusion/Exclusion							
Demographics & Baseline Disease Characteristics							
Prior and Concomitant Medications	X	X	X				
Medical History							
Height[e]	X	X	X	X	X	X	X
Weight in Clinic			X		X		
Weight at Home							
Dispense Weight & Study Drug Diary							
Collect/Review Weight & Study Drug Diary							
ECG			X		X		
Echocardiogram[f]							
Vital Sign Measurements			X		X		
Comprehensive Physical Exam			X		X		
Targeted Physical Exam							
Pregnancy Test for WOCBP[h]			X		X		
Study Drug Administration							
Dispense Study Drug							
Collect Study Drug							
Telephone Contact							
Adverse Event Collection	X	X	X	X	X	X	X
Kidney Ultrasound[j]							
Clinical Chemistry (incl. eGFR) [k]	X	X	X	X	X	X	X
BNP and NT-proBNP			X		X		
Hemoglobin A1c							
Hematology			X		X		
Coagulation			X		X		
Basic Lipid Panel			X		X		
Urinalysis and Microscopy			X		X		
Urine Collection for ACR[l]			X		X		
[redacted]							
Virus Serology							
PK Samples [n]	X		X		X		
SARS-CoV-2 Antibody Test					X		
Ambulatory Blood Pressure Monitoring [o]							
Tanner Staging [q]					X		

Abbreviations: ABPM = ambulatory blood pressure monitoring, ACR = albumin to creatinine ratio, ADPKD = autosomal dominant polycystic kidney disease, AE = adverse event, BNP = B-type natriuretic peptide, [redacted], , ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, IRB/EC = institutional review board/ethics committee, IWRS = Interactive Web Response System, NT-proBNP = N-terminal pro-brain natriuretic peptide, [redacted], PK = pharmacokinetic, SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2, Wk = week, WOCBP = women of child-bearing potential

[a] Total Screening period should not exceed 90 days.

[b] Screen B visit should be at least 1 day after Screen A and no more than 30 days prior to Day 1.

[c] Day 1 should be the day of randomization and administration of the first dose. Where randomization in the IWRS must occur earlier than Day 1, the Day 1 visit must align with the administration of the first dose. **On Day 1, all procedures must be performed before study drug administration.**

[d] Screening eligibility procedures do not need to be repeated on Day 1; however, a review of any changes in eligibility criteria should be evaluated prior to Day 1 procedures

[e] Height will be recorded in centimeters. Adult patients (18 ≤ age ≤ 70 years at Screen A visit) will be measured at Screen A only. Adolescent patients (12 ≤ age < 18 years at Screen A visit) will be measured at all specified timepoints.

[f] An echocardiogram performed during screening or within 6 months prior to Day 1 may be used to determine eligibility.

[g] Screen B vital sign measurements are needed only if re-assessing blood pressure for eligibility.

[h] A serum pregnancy test will be performed at the Screen A visit for WOCBP or at any point in time if a pregnancy is suspected. All other pregnancy assessments will be urine pregnancy tests. Additional pregnancy assessments will be performed more frequently if required by local law or requested by local regulatory authorities or IRBs/ECs.

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

[j] Kidney ultrasound (historical or one obtained during screening) may be used to diagnose ADPKD for patients without a prior ADPKD diagnosis.

[k] eGFR will be calculated and appear on lab reports for Screen A and Screen B visits, eGFR will no longer be calculated for any visits after the Screening period.

[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.

[redacted]

[n] Patients must refrain from taking study drug prior to coming to the clinic for PK draws at Week 12 and Week 100.

[o] Ambulatory Blood Pressure Monitoring (ABPM) is an optional sub-study for adult patients (18 ≤ age ≤ 70 years at Screen A) who enroll under protocol version 6.0 (or greater) and consent to the procedure prior to randomization. See Section 9.10.33 for details and timing on ABPM. ABPM will not be performed on adolescent patients (12 ≤ age < 18 years at randomization

[p] For patients who consent to the optional ABPM sub-study, the initial (baseline) 24-hour monitoring assessment must be done during the Screening period prior to Day 1. See Section 9.10.33 for detailed information.

[q] Adolescent patients (12 ≤ age < 18 years at Screen A visit) will be assessed by Tanner staging at all specified timepoints.

[r] For adult patients who consent to the optional ABPM sub-study, the final 24-hour monitoring assessment occurs after Week 88 and prior to Week 100 (last dose). For patients who discontinue study drug prior to Week 100, patients who consented to ABPM should have the assessment at End of Treatment if no ABPM was conducted in the four weeks prior to the date of last dose.

[s] See Section 8.3.3 and Section 8.5.1 for details on the Off-Treatment Period.

[t] Unless permitted in the protocol, all study activities, including assessments and sample collection, are expected to be completed on the same day (i.e., day of the visit).

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Inclusion Criteria

NOTE: Participating sites in Australia will only treat adult patients, defined as 18 years old or older at the time of consent.

Diagnosis and main criteria for inclusion:

1. Male and female patients 12 ≤ age ≤ 70 upon study consent;
2. Diagnosis of ADPKD
    a. For adult (18 ≤ age ≤ 70 years) diagnosis of ADPKD by modified Pei-Ravine criteria:
        i. at least 3 cysts per kidney by sonography or at least 5 cysts by CT or MRI with family history of ADPKD or
        ii. at least 10 cysts per kidney by any radiologic method and exclusion of other cystic kidney diseases if without family history;
    b. For adolescent (12 ≤ age < 18 years) diagnosis of ADPKD by:
        i. the presence of family history and/or genetic diagnosis and the presence of at least 1 cyst of 0.5 cm on ultrasound or MRI,
        ii. patients without a family history or genetic diagnosis must have at least 10 bilateral renal cysts in total, and exclusion of other cystic kidney diseases;
3. eGFR must:
    a. Have a percent difference ≤ 25% at screening (the values at Screen A and Screen B), and;
    b. Have an average (the values at Screen A and Screen B) ≥ 30 to ≤ 90 mL/min/1.73 m^2 for patients 12 to 55 years or ≥ 30 to ≤ 44 mL/min/1.73 m^2 for patients 56 to 70 years, and;
    c. Support ADPKD disease progression (i.e., average yearly eGFR decline of ≥ 2.0 mL/min/1.73 m^2 for the past two years) for patients with either screening eGFR ≥ 60 to ≤ 90 mL/min/1.73 m^2 or age 56 to 70 years (See Protocol Section 9.10.2)
4. ACR ≤ 2500 mg/g at Screen B visit;
5. Systolic blood pressure ≤ 140 mmHg and diastolic blood pressure ≤ 90 mmHg at Screen A or Screen B visit after a period of rest. Patients receiving an angiotensin-converting enzyme (ACE) inhibitor and/or an angiotensin II receptor blocker (T2T)* must be on a stable dose for at least 6 weeks prior to the Screen A visit; *see Protocol Section 9.1.7.
6. 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), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ the upper limit of normal (ULN);

7. Able to swallow capsules;
8. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures;
9. Evidence of a personally signed and dated informed consent/assent document indicating that the patient has been informed of all pertinent aspects of the study prior to initiation of any protocol-mandated procedures.
10. Patients receiving an SGLT2 inhibitor must be on a stable dose for at least 4 weeks prior to the Screen A visit;

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. Use of tolvaptan within 2 months prior to Screen A. Initiation of concomitant tolvaptan use during the study is not permitted;
3. History of administration of polycystic kidney disease-modifying agents (somatostatin analogues) within 2 months prior to the Screen A visit;
4. B-type natriuretic peptide (BNP) level > 200 pg/mL at Screen A visit;
5. Uncontrolled diabetes (HbA1c > 11.0%) at Screen A visit;
6. Serum albumin < 3 g/dL at Screen A visit;
7. History of intracranial aneurysms;
8. Kidney or any other solid organ transplant recipient or a planned transplant during the study;
9. Acute dialysis or acute kidney injury within 12 weeks 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 III or IV;
    h. History of untreated atrial fibrillation;
    i. History of unstable arrhythmias;
11. Systolic BP < 90 mm Hg at Screen A visit after a period of rest;

12. BMI < 18.5 kg/m^2 at the Screen A visit;
13. History of malignancy within 5 years prior to Screen A visit, with the exception of localized skin or cervical carcinomas;
14. Systemic immunosuppression for more than 2 weeks, cumulatively, within the 12 weeks prior to randomization or anticipated need for immunosuppression during the study;
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;
22. Coronavirus disease 2019 (COVID-19) pneumonia, related acute kidney injury, or related hospitalization within 6 months prior to Day 1.

8.3. Screening, Treatment, and Off-Treatment Periods

8.3.1. Screening Period

The screening period begins with the signing of the informed consent/assent form at the Screen A visit and ends at the start of the Day 1 visit. Where the signing of the informed consent/assent precedes the Screen A visit, the screening period is considered to begin at the Screen A visit. The duration of the screening period must not exceed 90 days. The Screen A procedures may be completed across multiple days. Efforts should be made to ensure the Screen B visit is no more than 30 days prior to Day 1.

Sites must not initiate screening of an adolescent who will become an adult prior to Day 1. If, prior to randomization, an adolescent patient who screened has become an adult, the patient must be screen-failed and rescreened, such that eligibility is assessed based on the adult eligibility parameters (ADPKD diagnosis and eGFR calculation).

Where calculation of the screening eGFR average results in a decimal, basic rounding principles apply. For example, an average eGFR of 29.5 mL/min/1.73 m^2 would round up to 30 mL/min/1.73 m^2.

Eligibility should be confirmed prior to randomization of any patient in the IWRS.

All screening procedures should be completed per the schedule of assessments in Table 4.

8.3.2. Treatment Period

The Treatment Period refers to the time from administration of the first dose (Day 1 visit) through administration of the last dose (Week 100 visit). Administration of the first dose of study drug should occur in-clinic, at the Day 1 visit, after confirmation of eligibility and

randomization. Administration of the last dose of study drug should occur in-clinic, at the Week 100 visit, following the collection of all lab and PK assessments.

During the treatment period, sites should ensure proper documentation of any intentional interruptions in dosing, including the reason for and duration of the interruption. Information regarding interruptions should be entered into the clinical database.

A patient who discontinues study drug early has a shortened treatment period. Regardless of when a patient's treatment period ends, it is imperative that an off-treatment period follows study drug discontinuation. See Section 8.3.3 for required assessments in the Off-Treatment Period.

If a patient resumes study drug, the patient should resume the normal study schedule and follow instructions in Section 9.11 regarding dose interruption and re-challenge.

All assessments during the Treatment Period should occur per the Schedule of Assessments, in Table 4.

8.3.3. Off-Treatment Period

The purpose of the Off-Treatment Period is to continue assessing patients for 12 weeks after patients have completed 100 weeks of study drug administration (or after the last dose of study drug if a patient discontinues study drug early). The Off-Treatment Period visits are of critical significance to this study. Every effort should be made to obtain off-treatment assessments following any discontinuation of study drug, whether at the planned Week 100 timepoint or at an earlier timepoint during the study.

For patients who remain on study drug through Week 100, the planned Off-Treatment Period begins the day after the Week 100 visit and continues through Week 112. Patients must complete 7 visits during the Off-Treatment Period, as listed in Table 4, and as described below:

- Week 103 visit (21 – 25 days from date of last dose)
- Week 104 A & B visits (28 – 36 days from date of last dose) at least one day apart
- Week 108 A & B visits (56 – 64 days from date of last dose) at least one day apart
- Week 112 A & B visits (84 – 92 days from date of last dose) at least one day apart

To the extent possible, sites should try to avoid bringing patients in very late in the window for a particular visit, and then very early in the window for the next timepoint. For example, a patient who completes Week 104 A & B visits 35 and 36 days after last dose, then completes Week 108 A & B visits 56 and 57 days after last dose, would have Week 104 and Week 108 visits spaced only 20 days apart, rather than ~4 weeks apart. Sites should attempt to achieve an approximate 4-week interval between Weeks 100, 104, 108, and 112.

For patients who discontinue study drug prior to Week 100, the patient should be assessed at the following timepoints, see Off Treatment Period in Table 4 for full list of assessments:

- An End of Treatment visit as close as possible to the last dose
- One visit 3 weeks after discontinuation (21 – 25 days from date of last dose)
- Two visits 4 weeks after discontinuation (28 – 36 days from date of last dose) at least one day apart
- Two visits 8 weeks after discontinuation (56 – 64 days from date of last dose) at least one day apart

- Two visits 12 weeks after discontinuation (84 – 92 days from date of last dose) at least one day apart

For patients who discontinue study drug early, after the above Off-Treatment Period is completed, the patient will continue with all assessments through Week 112, except PKs and ABPM (if applicable). See Section 8.5.1 for detail regarding the importance of continued follow-up for patients who discontinue study drug early.

AEs should be reported until the Week 112 (B) study visit. .

8.4. Patient Re-Screening & Re-Testing

8.4.1. Re-Screening

Patients may repeat Screening once to qualify for the study (re-screening must occur at least 2 weeks after the screen fail). In rare circumstances, a second re-screening may be appropriate; in these cases, the site must consult with the Medical Monitor for approval. When a patient repeats screening, the patient is given a new patient number and re-screening procedures are completed under the new patient number.

8.4.2. Re-Testing

In rare situations, a specific screening test (e.g., BNP) may be repeated if the test value is inconsistent with the patient's medical history and/or is considered by the investigator to be an anomaly. Medical Monitor approval must be obtained prior to re-testing any of the eligibility parameters for a patient.

8.5. Patient Discontinuation and Termination

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

8.5.1. Study Drug Discontinuation Criteria

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

- Adverse event;
- Death;
- Lost to follow-up;
- Physician decision;
- Pregnancy;

- Protocol specified criterion met (Section 7.4, Section 9.1.1, Section 9.1.9, Section 9.3.1, Section 9.6.1, Section 9.8.3);
- Withdrawal by patient;

To maximize patient retention and minimize missing data, patients who discontinue study drug early are encouraged to remain active in the study and complete all future study visits and assessments, except PKs and ABPM, if applicable.

For patients who discontinue treatment prior to Week 100, see Section 8.3.3 for the required off-treatment assessments. After the off-treatment assessments, the patient will continue with follow-up assessments through Week 112. The collection of laboratory data and vital status through Week 112 (B) is important for trial integrity, and data may be obtained through in-person clinic visits or through home health visits.

See Section 9.10.16 for Adverse Event Collection following study drug discontinuation.

For patients who are unwilling to complete all future visits, the Week 108 visit is of paramount significance. Collecting Week 108 data for all randomized patients is essential for trial integrity.

For patients who discontinue study drug and are no longer willing to return for all scheduled study visits, a number of follow-up options are available and must be discussed with the patient thoroughly, including:

- Participation in follow-up procedures specified in the protocol by an in-home visit, where feasible;
- Reduced in-person visit schedule;
- Telephone contact only;
- Contact of alternative person(s) who has been designated in source records as being available to discuss the patient's medical condition;
- Non-direct follow-up of patient information including obtaining additional information from the patient's medical records (e.g., ESKD or death).

These reduced follow-up options should be discussed with any patient considering study termination following discontinuation of study drug. The frequency and schedule of participation in follow-up procedures, whether in-clinic, by telephone, by in-home visit(s) or some other means, should be discussed and agreed to by patient and staff. All efforts to prevent the patient from progressing to a "Lost to Follow-Up" status must be made. Any discussions about reduced follow-up options must be documented in the patient's source file.

Sites should strongly consider the use of home health care visits to maximize data collected from patients who become unwilling or unable to return for in-clinic visits.

8.5.2. Study Termination Criteria

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

- Death;
- Lost to follow-up;

- Withdrawal of consent by patient.

Every reasonable effort should be made to contact patients who do not return for a scheduled visit. Follow-up options described in Section 8.5.1 should be discussed, as soon as possible, with patients who no longer wish to return for all scheduled in-person visits, patients who have failed to return for a scheduled visit, and patients who may be demonstrating an increasing risk of no longer communicating with the site. Patients should not be considered lost to follow-up until the scheduled Week 112 visit date.

The term "withdrawal of consent" should be used only when the patient no longer wishes to participate in the trial and no longer authorizes investigators to make efforts to continue to obtain their outcome data. Unless the patient provides written withdrawal of consent or there is other written documentation by the investigator confirming the patient's verbal intent to completely withdraw from the trial, patients should be followed for all protocol specified evaluations and assessments. The investigator should inquire about the reason for withdrawal of consent, request the patient return all unused investigational product, request the patient return for end-of-treatment and follow-up visits (if applicable), and follow-up with the patient regarding any unresolved AEs. Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent or assent, if applicable. The reasons for a patient's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the patient and the integrity of the trial. Only patients who withdraw permission for all follow-up options outlined in Section 8.5.1 are considered to have completely withdrawn their consent to participate in the study.

9. TREATMENT OF PATIENTS

9.1. Select Management Guidelines

The guidelines below apply to the management of study participants.

9.1.1. Management of Fluid Status

Specific risk 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 and rapid weight gain will also be used to monitor fluid status after randomization. Patients who experience a BNP > 100 pg/mL that represents a doubling (or more) of BNP levels from Day 1 should have an unscheduled telephone contact immediately to evaluate for any symptoms of fluid overload, and accordingly, request an unscheduled visit to assess signs and symptoms of congestive heart failure, heart failure, acute pulmonary edema, etc. identified through the telephone contact. In addition, patients will be given a Sponsor-provided scale to use at home to collect and record weights daily during the study. In the event the Sponsor-provided scale is temporarily unavailable (e.g., patient is traveling, replacement scale has not arrived to patient, etc.), patients may use any available scale. Use of a scale other than the Sponsor-provided scale should be documented in the patient diary. Patients who experience a weight increase of three pounds (1.4 kilograms) in a day or five pounds (2.3 kilograms) or greater increase within a week must have an unscheduled telephone contact immediately. Whether prompted by BNP elevations, sudden weight gain, or by the presence of clinical signs and symptoms the patient must be instructed to stop taking their study medication immediately and be medically evaluated by the investigator or a local physician within 1 to 2 days.

Investigators are encouraged to consider starting or increasing doses of diuretics (thiazides, loop diuretics) early after recognition of edema. This can be done concurrently with temporary discontinuation of the study drug. Patients may not restart their study medication 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 must immediately assess symptoms of fluid overload and determine appropriate medical management, as necessary, including whether stopping drug administration is required.

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

For only patients who enrolled under Version 2 of the protocol (only performed in the US at the beginning of the study) and are receiving tolvaptan (JYNARQUE), liver biochemistries (ALT, AST, and/or bilirubin levels) should be monitored according to the relevant package insert/REMS program for tolvaptan.

For all patients enrolled, nearly all instances of elevated transaminases due to bardoxolone methyl treatment are expected to be asymptomatic.

Some patients may experience more rapid increases in ALT/AST values than others during the dose titration period. Investigators may consider extending the time between each dose increase to manage ALT/AST elevations.

If a patient's transaminases are elevated, follow the instructions outlined in Table 5.

Table 5: Management of Elevated Transaminase Levels (ALT and/or AST)

<table>
<tr><th>ALT and/or AST Level(s)</th><th>Interrupt Dose?</th><th>Procedure</th></tr>
<tr><td>> 8x ULN</td><td rowspan="4">Yes</td><td rowspan="4">➢ Discontinue study drug temporarily
➢ Contact the Medical Monitor

Study drug may be restarted with Sponsor approval after all the following criteria are met:
• Ultrasound or MRI of the hepatobiliary tree*;
• ALT and AST returned to ≤ ULN;
• TBL is within normal range;
• Other relevant labs (e.g., albumin, INR, PT) are within normal range;
• No clinical signs or symptoms of liver injury are present.

*Based on imaging results, if additional tests/studies are warranted, this should be discussed with the Medical Monitor.</td></tr>
<tr><td>> 5x ULN for more than 2 weeks</td></tr>
<tr><td>> 3x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia</td></tr>
<tr><td>> 3x ULN <u>and</u>
(TBL > 2X ULN <u>or</u> INR > 1.5)</td></tr>
<tr><td>> 3x ULN</td><td>No</td><td>➢ Check transaminase levels (as well as TBL, GGT, ALP, and INR) within 48 to 72 hours

Continue testing for ALT/AST every 72 to 96 hours until transaminase levels are below 3X the ULN for at least one week</td></tr>
<tr><td colspan="3">ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma-glutamyl transpeptidase, INR = international normalized ratio, MRI = magnetic resonance imaging, PT = Prothrombin Time, TBL = total bilirubin, ULN = upper limit of normal</td></tr>
</table>

Patients who meet the interruption criteria outlined above must restart study drug at the 5 mg dose level and dose titrate according to Section 7.3.3.

9.1.3. Management of Muscle Spasms

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

9.1.4. Weight Loss

Adults - The investigator should evaluate a patient for unexplained weight loss of 7% or greater from the Day 1 weight. Ongoing assessments of other symptomology (for example: nausea, vomiting, abdominal pain or poor appetite) may be warranted to ensure the patient is receiving adequate nutrition and evaluate for other causes of weight loss.

Adolescents - If weight loss of greater than 5% from the Day 1 weight is observed, the investigator should temporarily stop study drug, and evaluate the patient for any symptomology (for example: nausea, vomiting, abdominal pain or poor appetite) leading to weight loss, and/or other causes of weight loss. The investigator should inform the Medical Monitor prior to stopping study drug, and the investigator and Medical Monitor should discuss management of the patient.

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 for 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 and should consult the Medical Monitor for appropriate measures.

9.1.7. Management of Blood Pressure

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

Patients being treated with an ACE inhibitor and/or ARB should be receiving the maximally tolerated labeled daily dose (MTLDD), defined as the dose at or below the labeled dose that does not exhibit any intolerable adverse effects (e.g., hypotension, hyperkalemia), based on the investigator's assessment. If the patient is currently receiving one drug (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 reasonable.

9.1.9. End Stage Kidney Disease

Patients approaching end stage kidney disease (ESKD) should be closely monitored by the investigator to fully characterize their progression. For patients with eGFR $\leq$ 15.0 mL/min/1.73 m^2 (as calculated by the site, using the central lab-provided serum creatinine and the formulas provided in Section 9.10.18.1), initiate more frequent follow-up to closely monitor safety assessments (i.e., clinical chemistry (incl. eGFR), hematology, vital sign assessments (incl. weight), BNP and NT-proBNP). Similar frequent follow-up may also be implemented for patients with eGFR > 15.0 mL/min/1.73 m^2 who, in the investigator's opinion based on the anticipated progression of their disease, may be approaching ESKD. Patient follow-up should be completed in-person or through a home health visit where in-person visits are not feasible, at least once every 4 weeks (± 2 weeks), until one of the following occurs:

- Initiation of dialysis;
- Receipt of transplant.

Two off-treatment serum creatinine assessments should be collected 28 to 36 days after last dose, and prior to initiation of dialysis or receipt of transplant. Upon initiation of dialysis, study drug should be interrupted. Because laboratory and vital sign assessments can be affected by receiving dialysis, those safety assessments should not be performed concurrently while a patient is receiving dialysis. Patients receiving dialysis should continue to be followed for vital status and SAEs by phone or in-person according to the protocol scheduled visits. Dialysis not lasting at least 12 weeks will be considered acute dialysis, and patients should be considered for re-initiation of study drug with Medical Monitor approval. Such patients should continue to undergo frequent follow-up (i.e., at least once every 4 weeks (± 2 weeks)) while eGFR $\leq$ 15.0 mL/min/1.73 m^2. Study drug may be re-started following acute dialysis, with Medical Monitor approval. Dialysis lasting at least 12 weeks will be confirmed as maintenance dialysis. Upon confirmation of maintenance dialysis, study drug should be discontinued.

Upon receipt of kidney transplant, study drug should be discontinued.

Following study drug discontinuation due to confirmation of maintenance dialysis or receipt of kidney transplant, patients should continue to be followed only for vital status and SAEs by phone or in person according to the planned contact schedule in Section 7.5 through their scheduled Week 112 visit date. See Section 8.5 for description of follow-up options following study drug discontinuation. Initiation of dialysis (acute and/or maintenance) and receipt of kidney transplant due to end stage kidney disease should be considered important medical events, and as such recorded as SAEs.

9.1.10 Monitoring Growth and Sexual Development in Adolescents

Growth and sexual development will be assessed through an evaluation of height, weight, and Tanner Staging. See the Study Reference Manual for details on the Tanner staging.

Body weight should be measured daily by patients/caregivers using a provided weighing scale. Weight and height will also be measured at all site visits, as outlined in Section 9.10.7. Patients should be instructed to inform the site if there is an observed weight loss of more than 3 pounds (1.4kg) in between clinic visits (Section 9.1.1).

The Medical Monitor will routinely evaluate both weight and height entered into the clinical database of adolescents and will inform the investigator to initiate further evaluation if there is a weight loss of ≥5% or lack of expected growth per growth charts.

Sexual maturity will be assessed by the investigator using Tanner Staging. If any abnormal patterns of sexual maturity are identified on evaluation of Tanner Staging, the Medical Monitor should be notified for additional discussion.

9.2. Description of Study Drug

Bardoxolone methyl (RTA 402) drug product information is shown in Table 6. Information about the placebo is shown in Table 7.

Table 6: Bardoxolone Methyl Drug Product Information

Description	Bardoxolone methyl capsule (5 mg, 10 mg, 15 mg, 20 mg)
Ingredients	Bardoxolone methyl Methacrylic Acid – Ethyl Acrylate Copolymer (1:1), Type A Silicified Microcrystalline Cellulose Hydroxypropyl Methylcellulose Lactose Monohydrate Sodium Lauryl Sulfate Colloidal Silicon Dioxide Magnesium Stearate Gelatin capsules Titanium Dioxide (capsule pigment)
Route of Administration	Oral

Table 7: Placebo Information

Description[a]	Placebo for bardoxolone methyl capsule (size #4, size #2, size #1, and size #0)
Ingredients	Silicified Microcrystalline Cellulose Lactose monohydrate Magnesium Stearate Gelatin capsules Titanium Dioxide (capsule pigment)
Route of Administration	Oral

[a] Placebo capsules are size matched to the corresponding active dose capsule

9.3. Concomitant Medications

9.3.1. Excluded and Prohibited Medications

9.3.1.1. Excluded Medications

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

- Tolvaptan (patients on tolvaptan who have already enrolled under Version 2 of the protocol may remain in the trial);
- Somatostatin analogues
- Any other investigational drug or device as part of an interventional study within 30 days prior to Day 1;
- Chronic (> 2 weeks) immunosuppressive therapy, or need for corticosteroids, including therapies such as glucocorticoids, oncologic preparations, and anti-TNFα agents [e.g., infliximab (Remicade®), adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®)] within 12 weeks prior to randomization. Glucocorticoid intra-articular injections, inhaled products, topical preparations, and nasal preparations are allowed.

If a patient takes an excluded medication during the study, the investigator should consult with the Medical Monitor immediately to discuss if there is need for study drug interruption or discontinuation.

9.3.1.2. Prohibited Medications

Concomitant use with strong and moderate CYP3A4 inhibitors is prohibited, switching to alternate allowed medication should be considered. If a strong or moderate CYP3A4 inhibitor is medically necessary, discuss with Medical Monitor. Patients who are using these medications prior to screening should have a washout for at least 5-half-life's or 30 days whichever is longer.

Concomitant use with strong and moderate CYP3A4 inducers is prohibited, switching to alternate allowed medication should be considered. If a strong or moderate CYP3A4 inducers is medically necessary, discuss with the Medical Monitor. Patients who are using these medications prior to screening should have a washout for at least 5-half-life's or 30 days whichever is longer.

Concomitant use with chronic (> 2 weeks) immunosuppressive therapy (corticosteroids, including therapies such as glucocorticoids, oncologic preparations, and anti-TNFα agents [e.g., infliximab (Remicade®), adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®)]) is prohibited.

Concomitant use with tolvaptan, somatostatin analogues, and any other investigational drug or device is prohibited. Concomitant dosing with prohibited medications is not allowed and will not be approved by the Medical Monitor. If a site becomes aware of a patient administering a prohibited medication, the Medical Monitor should be notified immediately to determine whether study drug should be permanently discontinued or whether an interruption is appropriate.

To minimize missing data and to maintain study integrity, patients who must take prohibited medications during the study should continue follow-up visits, even after study drug discontinuation, unless directed otherwise by the Medical Monitor. Certain prohibited medications (e.g., tolvaptan) will warrant termination from the study, due to the potential for the concomitant medication to confound the interpretation of study data.

Sites must avoid initiation of prohibited medications until all Off-Treatment assessments are completed (approximately 12 weeks following the patient's last dose of study drug).

If a patient permanently discontinues study drug and continues being followed in the study, the administration of a prohibited medication is no longer considered a protocol deviation after 12 weeks following the patient's last dose of study drug. Beginning 12 weeks after the patient's last dose, administration of a prohibited medication does not require input from the Medical Monitor.

Importantly, the administration of any medications listed in this section should be recorded in the concomitant medication page of the EDC independent of the patient's study drug status or duration since the patient's last dose of study drug, in order to ensure accurate interpretation of safety and efficacy data.

9.3.2. Permitted Medications

Allowed concomitant medications include the following:

- Antibiotics, including (but not limited to) fluoroquinolones and trimethoprim-sulfamethoxazole (if the antibiotic being prescribed is a moderate or strong CYP3A4 inhibitor or inducer, see Section 9.3.1.2.
- Daily multivitamins or recommended daily supplements;
- Other medications intended to manage concurrent diseases, as authorized by the treating physician;
- Statins (e.g., pravastatin or rosuvastatin), in the Czech Republic and globally;
- Pain management: acetaminophen, and other adjuvant analgesics and opioids may be used as deemed appropriate by the investigator, in the Czech Republic and globally;
- Oral, implantable, or injectable contraceptives ;
- Glucocorticoid intra-articular injections, inhaled products, topical preparations, and nasal preparations.

Patients taking medication chronically, including ACE inhibitors, ARBs, and SGLT2 inhibitors 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.

The list presented above is meant to serve as a broad guideline and is not exhaustive. Drugs not listed here, but which are deemed medically necessary, may be used provided if they do not fall under the excluded medications described in Section 9.3.1. Questions about permitted medications should be directed to 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. Patients should administer study drug exactly as instructed by the site. Non-compliance is defined as taking less than 80% or more than 110% of expected study medication during any evaluation period (visit to visit). A lack of treatment compliance during any evaluation period (visit to visit) should be entered as a protocol deviation.

Patients should record in the patient diary all administered and missed doses of study drug. The reason for a missed dose should be recorded in the patient diary. Missing dose includes inadvertent missed doses as well as study drug interruptions and discontinuations. Patients will be asked to return all unused study drug (study drug bottles and any unused capsules). The study drug must not be used for reasons other than that described in the protocol.

9.5. Randomization

An IWRS will be utilized to randomize patients 1:1 to bardoxolone methyl or placebo. Randomization will be stratified by eligibility eGFR category (30 to <60; ≥60 to 90), concomitant tolvaptan use (yes, no), and screening ACR (≤300 mg/g, >300 mg/g). Eligibility eGFR is the average of Screening eGFR visits.

Randomization should occur on Day 1, as a Day 1 study procedure. Where this is not possible, due to logistical issues at the site, and randomization occurs prior to Day 1, this will result in a

protocol deviation. When randomization occurs prior to Day 1, the site must confirm eligibility prior to randomizing the patient in the IWRS and again prior to dispensation of IP at the Day 1 visit.

9.6. Blinding

All patients, investigators, site personnel, laboratories, and central readers with direct involvement in the conduct of the study or their designees will be blinded to treatment assignments throughout the trial. To prevent potential bias, appropriate measures will be taken to ensure the blind is maintained for the patients and personnel. To maintain the blind, investigators will distribute blinded study drug treatment kits to patients as directed by the IWRS system. Investigators and patients will not be blinded to dose level, but will be blinded to treatment assignment (i.e., bardoxolone methyl vs. placebo).

An IWRS will manage treatment assignments and dose-titration. The only people with direct access to treatment assignments will be those individuals who develop and maintain the randomization code, the Data Monitoring Committee (DMC), and the statistical group reporting to the DMC.

9.6.1. Patient Unblinding

Although bardoxolone methyl has no known antidote, under rare circumstances unblinding may be considered medically necessary.

The investigator is encouraged to contact the Medical Monitor to discuss situations in which he or she believes that the blind should be broken, but the investigator has the right to break the blind (e.g., in the event of a serious or life-threatening medical situation). If unblinding is required, the investigator will utilize the IWRS to perform the unblinding. If a study drug assignment is unblinded, the investigator must describe the event that required unblinding in the patient's source documents.

Patients must discontinue taking study drug if their treatment assignment has been unblinded to the investigator (or designee). Such patients must undergo the same study drug discontinuation procedures as those patients who discontinue taking study drug for other reasons. Following study drug discontinuation due to unblinding, patients should continue with study follow-up through their scheduled Week 112 visit date for vital status only.

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

9.6.2. Unblinding for Regulatory Submission

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

9.6.3. Data Monitoring Committee

An independent DMC will review unblinded safety data throughout the study and make recommendations as appropriate. The DMC will begin data reviews approximately 3 months after the first patient is enrolled and continue regular reviews through the last dose of the last patient enrolled.

The DMC will consist of external experts supported by an independent statistical group which will prepare unblinded analyses for the DMC and will have no role in the statistical analysis plan (SAP) after the study has started enrolling patients. A separate statistical group not associated with the DMC will be responsible for producing and finalizing the SAP and executing the final data analysis of the study.

The DMC will be governed by a charter that will describe the following:

- Roles and responsibilities of the DMC members and the independent statistical group;
- Meeting format and frequency;
- Communication channels between the DMC, the independent statistical group, the Sponsor, and the blinded study statisticians;
- Voting process and requirements (e.g., requirement of consensus for issuance of a termination recommendation);
- Provisions governing conflict of interest and confidentiality.

Briefly, the DMC will review the progress of the study and the accumulating unblinded data while the study is ongoing. The DMC will make recommendations to Sponsor representatives following each meeting. The DMC may recommend the study continue as is, be modified to protect patient safety, or be terminated for safety. The DMC is not expected to make recommendations for the trial based specifically on the analysis of the primary endpoint. Investigators, not the DMC, will make intra-patient dose-escalation decisions.

9.7. Unscheduled Visits

Unscheduled visits may be performed at any time and for any reason, including those not specifically mentioned in this section, as deemed necessary by the investigator.

Unscheduled visits conducted for the following reasons should include collection of AEs, clinical chemistry, BNP/NT-proBNP, hematology, concomitant medication collection, and vital signs:

- 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;
- Resuming study drug following an extended interruption;

- eGFR ≤15.0 per Section 9.1.9;
- Patient safety evaluation.

Unscheduled visits conducted for the following reasons do not require additional assessments unless deemed necessary by the investigator:

- Study drug dispensation;
- Placement or return of ABPM monitor;
- Any operational need that would require the patient to return to the site between scheduled visits.

9.8. Pregnancy

9.8.1. Women of Childbearing Potential and Fertile Males

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

For patients enrolled in United Kingdom, women with bilateral tubal ligation are considered as WOCBP and will be required to use other types of birth control measures specified in Section 9.8.2.

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

Czech Republic Only:

Women of childbearing potential (WOCBP) are those who have experienced menarche and are not surgically sterile (no history of bilateral tubal ligation, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), and are not postmenopausal (defined as no menses for at least 1 year without an alternative medical cause).

Fertile males are those who have entered puberty or reached physical maturation (after puberty) and are not surgically sterile (no history of bilateral orchiectomy)

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)) Double-barrier methods are not allowed for patients at participating sites in Germany and Australia;

- Use of hormonal contraceptives (oral, parenteral, intravaginal, or transdermal) for at least 60 days prior to start of study drug administration;
- Use of an intrauterine device;
- Vasectomized partner (with vasectomy performed at least 6 months prior to screening with the appropriate post-procedure documentation of surgical success). Partner *must* be the sole partner for that patient;
- Abstain from sexual intercourse completely. Complete abstinence from heterosexual intercourse is only acceptable if it is the preferred and usual lifestyle of the individual. Periodic abstinence is not permitted.

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

- Use double barrier contraception method, defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream, diaphragm (always use with spermicidal jelly/cream)). Double-barrier method is not allowed for patients at participating sites in Germany and Australia:
- Have had a vasectomy (with vasectomy performed at least 6 months prior to screening with the appropriate post-procedure documentation of surgical success) (not permitted in the United Kingdom)
- Partner contraception methods; *must* be the sole partner for that patient:
  - Use of an intrauterine device;
  - Use of hormonal contraceptives (oral, parenteral, intravaginal or transdermal) for at least 60 days prior to start of study drug administration;
  - Surgically sterile partner (bilateral tubal ligation, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy); fallopian inserts with confirmed blockage (e.g., x-ray, ultrasound) (not permitted in the Czech Republic);
  - Reproductive potential has been terminated by radiation (not permitted in the Czech Republic);
  - Postmenopausal (defined as no menses for at least 1 year) without an alternative medical cause.
- Abstain from sexual intercourse completely. Complete abstinence from heterosexual intercourse is only acceptable if it is the preferred and usual lifestyle of the individual. Periodic abstinence is not permitted.

9.8.3. Suspected Pregnancy

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

If a WOCBP 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 WOCBP patient must 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 she consents to be followed), 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 study drug after an interruption will follow Section 9.11 for dose management and Table 4 for study schedule.

9.10. Study Procedures

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

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

Every effort should be made to ensure all assessments are conducted at in-person visits. In certain cases, and with prior sponsor approval, if a patient is unable or unwilling to come to the clinic for in-person assessments, the conduct of study procedures by home health nurses is permissible and should be considered as an alternative to a missed or skipped visit.

9.10.1. Informed Consent and Assent

Written informed consent (see Section 15.3) must be obtained from the patient before any study-related procedures are performed. Re-consenting will be required when there is an update or change in the study procedures, safety information, or any other information that may affect the patient's willingness to participate.

For adolescent patients, informed consent will be obtained from the parent(s) or legal guardian in accordance with regional laws or regulations. In addition, dependent upon the patient's age and IRBs, IEC, and/or local requirements, assent of the patient must also be obtained. Adolescent patients may be asked to personally sign and date either a separately designed, written assent form, or the written informed consent.

Patients who chose to participate in the Ambulatory Blood Pressure Monitoring sub-study will need to provide written informed consent prior to performing any assessments associated with ABPM.

Patients who chose to participate in blood and urine biobanking collection will need to provide written informed consent prior to performing any assessment associated with the specimen collection.

9.10.2. Inclusion/Exclusion

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

Inclusion 2b, which references genetic diagnosis, may be satisfied by either PKD1 and/or PKD2 gene mutation.

Inclusion 3c must show disease progression using average yearly eGFR decline of ≥ 2.0 mL/min/1.73 m^2 from the past two years. If a patient has limited historical eGFR values from the past two years, the investigator must discuss the patient's eligibility with the Medical Monitor.

Historical eGFRs used to determine eligibility must be well documented in the patient's source.

9.10.3. Demographics and Baseline Disease Characteristics

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

9.10.4. Prior and Current Concomitant Medications

The name, dose, and frequency must be recorded for all medications 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. Prior and concomitant medications (i.e., medications that the patient is taking or has taken within 30 days prior to Day 1) will be reviewed as indicated in Table 4. All medications will be recorded through the Week 112 visit as indicated in Table 4.

For patients who remain on study drug, the administration of any medications should be recorded in the concomitant medication page of the EDC through Week 112,

For patients who discontinue study drug early and continue to be followed in the study, all concomitant medications should be recorded for 12 weeks following the patient's last dose of study drug. Beyond 12 weeks after the patient's last dose, only those medications that are relevant to the clinical condition including kidney disease or that may have a potential impact on

kidney function must be recorded in the concomitant medication page of the EDC. Unscheduled phone visits may be used, as necessary, to ensure accurate collection of concomitant medications of interest.

Importantly, the administration of any medications listed in Section 9.3.1.2 (Prohibited Medications) should be recorded in the concomitant medication page of the EDC independent of the patient's study drug status or duration since the patient's last dose of study drug, in order to ensure accurate interpretation of safety and efficacy data.

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 includes the collection of historical serum creatinine values for the purpose of calculating historical eGFR values. Where possible, sites should obtain historical lab reports from the patient, and enter into the EDC approximately one historical value per year, for the prior 5 years. Medical history will be recorded as indicated in Table 4.

9.10.6. Height

Height should be measured without footwear or prosthetics using a wall-mounted stadiometer if performed in-clinic. For adult patients ($18 \leq$ age ≤ 70 years at Screen A visit), height is measured at Screen A. Adolescent patients ($12 \leq$ age < 18 years at Screen A visit), height is measured at the timepoints specified in Table 4,when in clinic visits are not possible, home health nurses should be used (see Appendix 2).

Height should be recorded in centimeters, and where height is measured in inches, the following formula should be used to convert inches to centimeters:

$$\text{Height (in inches)} \times 2.54 = \text{Height (in centimeters)}$$

Any conversions of units should be documented in the source documents.

9.10.7. Weight and Body Mass Index (BMI)

Weight must be measured as indicated in Table 4. BMI will be calculated in the eCRF each time the weight is recorded. The Sponsor will provide 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. In the event the Sponsor-provided scale is temporarily unavailable (e.g., patient is traveling, replacement scale has not arrived to patient, etc.), patients may use any available scale. Weights recorded in patient diaries will not be entered in the eCRF. Weights should be taken at approximately the same time each day and recorded in a patient diary. During study, weights will be recorded daily. Missing more than 20% of expected weight records in the patient diary during any evaluation period (visit to visit) is considered as non-compliance, which should be reported as a deviation. Patients will be instructed to stop administering study drug and contact the investigator if their daily weight increases per the criteria outlined in Section 9.1.1. Patients will be provided instructions within the Informed Consent Form and/or Assent Form to help ensure consistent weight collection throughout the study.

Weight should be recorded in kilograms, and where weight is measured in pounds, the following formula should be used to convert pounds to kilograms:

Weight (in pounds) ÷ 2.205 = Weight (in kilograms)

Any conversions of units should be documented in the source documents.

9.10.8. Electrocardiograms (ECG)

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

9.10.9. Echocardiogram

An echocardiogram will be recorded as indicated in Table 4 to determine patient eligibility. The echocardiogram may be performed during the Screening Period, or an historical echocardiogram may be used if it was performed within 6 months prior to Day 1.

9.10.10. Vital Sign Measurements

Vital sign measurements include the patient's pulse rate (beats/minute taken for at least 15 seconds), respiration rate, blood pressure, and body temperature. Vital sign measurements should be taken as indicated in Table 4.

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. For specific guidance related to blood pressure measurement, please see the Study Reference Manual.

9.10.11. Comprehensive Physical Examination & Targeted Physical Examination

Physical examinations must be performed by a physician, physician assistant, or registered nurse practitioner.

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

Targeted physical examinations are symptom-directed examinations and involve the organ system(s) associated with the symptoms exhibited or reported. Targeted physical examinations are to be performed at visits indicated in Table 4. If the investigator observes no symptoms that warrant further examination, the investigator may forego a more detailed physical examination, and the targeted physical examination may be considered complete.

9.10.12. Pregnancy Test

WOCBP (see Section 9.8) will complete a pregnancy test as indicated in Table 4, or at any time if pregnancy is suspected. Negative test results are required on Day 1 before study drug administration. 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.

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

9.10.13. Study Drug Administration

For dose levels up to 20 mg, patients should self-administer one capsule orally once a day beginning on Day 1 (in clinic) through the end of the Treatment Period, as indicated in Table 4. Patients who dose escalate to 30 mg should administer two capsules orally once a day. Each dose of study drug should be administered at approximately the same time each day. Study drug administration should be recorded in a patient diary through Week 100.

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.

Refer to Section 9.4 and 9.11 for treatment compliance and detail in dose management.

9.10.14. Study Drug Dispensation and Collection

Study drug will be dispensed to the patient and collected from the patient as indicated in Table 4. The patient will be dispensed the appropriate number of treatment kits at each timepoint: Day 1, Week 2, Week 4, Week 6, Week 8, Week 12, Week 24, Week 36, Week 48, Week 52 (B), Week 64, Week 76, and Week 88. If the patient is provided more than one kit, only one treatment kit should be opened at a time. Dispensed treatment kits from each visit (including unscheduled visits) should be returned to the site for collection as indicated in Table 4 or at the subsequent visit.

If the appropriate number of treatment kits (e.g., a 3-month supply) cannot be dispensed as outlined in Table 4, a partial supply may be provided to the patient. The remainder may be provided separately to the patient. Every effort should be made to avoid interruptions in dosing.

9.10.15. Telephone Contact

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

9.10.16. Adverse Event Collection

Patients will be observed for general appearance, presence of illness or injury, or signs indicative of a concurrent illness as indicated in Table 4. Patients must be instructed to volunteer any information regarding AEs on or after the first dose of study drug, or sites may 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.

AEs should be reported from the time of the first dose until the Week 112 (B) visit as indicated in Table 4.

For patients who discontinue study drug early (prior to Week 100) and continue to be followed in the study, all AEs should be recorded for 12 weeks following the patient's last dose of study drug. Beyond 12 weeks after the patient's last dose, only those AEs that are relevant to the clinical condition including kidney disease, may have an impact on kidney function, or may impact the interpretation of safety or efficacy data must be recorded in the AE log within the EDC. Unscheduled phone visits may be used, as necessary, to ensure accurate collection of AEs of interest.

AEs that are related to study procedures should be recorded in the AE log within the EDC independent of the patient's study drug status or duration since the patient's last dose of study drug.

See Section 11 for more detail regarding adverse events.

9.10.17. Kidney Ultrasound

Kidney ultrasound (historical or an ultrasound performed at Screen A) may be used to diagnose ADPKD. Patients with prior diagnosis of ADPKD will not have a kidney ultrasound performed as part of the study but must provide documentation of ADPKD diagnosis for eligibility.

9.10.18. Virus Serology

Blood samples will be collected for testing for hepatitis B and hepatitis C as indicated in Table 4. 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.

9.10.19. Clinical Chemistry

Samples will be collected for the following clinical chemistry analyses as indicated in Table 4: 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.

9.10.19.1. eGFR

The equation used to calculate eGFR for each patient (CKD-EPI or Bedside-Schwartz) is based on the patient's age at the time of consent/assent (generally the Screen A visit). For Adults (≥ 18 years ≥ 70 years) eGFR will be calculated by a central laboratory at the Screen A and Screen B visits using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation:

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

For Adolescents (≥12 and < 18 years):

- eGFR will be calculated by a central laboratory at the Screen A and Screen B visits using the Bedside Schwartz equation:

  eGFR (mL/min/1.73 m^2) = (0.41 × Height in cm) / S_{cr}

Where S_{cr} is serum creatinine (mg/dL), κ is 0.7 for females or 0.9 for males, and α is -0.329 for females or -0.411 for males. Min indicates the minimum of S_{cr}/κ or 1 and max indicates the maximum of S_{cr}/κ or 1. Age indicates age at time of lab collection.

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

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

X=1st eGFR value (Screen A)

Y=2nd eGFR value (Screen B)

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

In the absence of any clinically significant event or other medical conditions, the investigator should consider re-testing eGFR if the most recent value is significantly different from the prior value.

9.10.20. 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 4. 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 the Central Laboratory Manual provided to the investigator.

9.10.21. Hemoglobin A1c

Samples will be collected for hemoglobin A1c as indicated in Table 4. Detailed instructions on collection, storage, and shipment of the samples will be provided in the Central Laboratory Manual provided to the investigator.

9.10.22. Hematology

Samples will be collected for the following hematology assessments as indicated in Table 4: hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, neutrophils, bands (if detected), lymphocytes, monocytes, basophils (if detected), eosinophils (if detected), absolute platelet count, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC).

9.10.23. Coagulation

Samples will be collected for the following coagulation assessments as indicated in Table 4: Prothrombin Time (PT) and International Normalized Ratio (INR). The coagulation assessments were added to the schedule of assessments through a protocol amendment. Sites should collect these samples from patients once the central laboratory kits and database enable collection. Until such time the site can collect this test, failure to collect it is not considered a protocol deviation.

9.10.24. Lipid Panel

Samples will be collected for the following lipid assessments as indicated in Table 4: Total Cholesterol, Low-Density Lipoprotein (LDL), High-Density Lipoprotein (HDL), and Triglycerides.

The lipid panel was added to the schedule of assessments through a protocol amendment. Sites should collect these samples from patients once the central laboratory kits and database enable collection. Until such time the site can collect this test, failure to collect it is not considered a protocol deviation.

9.10.25. SARS-CoV-2 Antibody Testing

Samples will be collected for SARS-CoV-2 antibody testing as indicated in Table 4.

The SARS-CoV-2 antibody testing was added to the schedule of assessments through a protocol amendment. Sites should collect these samples from patients once the central laboratory kits and database enable collection. Until such time the site can collect this test, failure to collect it is not considered a protocol deviation.

9.10.26. Urinalysis and Microscopy

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

9.10.27. 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 4. Appropriate containers for the collection will be provided to the patient at the visit prior to the collection.

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

[redacted]

[redacted]

[redacted]

[redacted]

9.10.32. Pharmacokinetic (PK) Blood Samples

Blood samples for determination of plasma bardoxolone methyl and potential metabolite concentrations will be drawn as indicated in Table 4.

Patients must provide the time of their last two doses of study drug.

PK blood sample collection instructions should be referenced in the Central Laboratory Manual.

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.

Patients who have discontinued study drug should not complete PK procedures

<u>Week 12 PK</u>

If sites or patients are unable to perform the required PK assessments at the Week 12 visit, these PK assessments may be collected at Week 24, Week 36, or Week 48.

Patients must refrain from taking study drug prior to coming to the clinic for the Week 12 visit, as patients will administer study drug in-clinic as instructed by the site. Patients must provide the time and date of the two most recent doses of study drug, prior to the blood samples being collected.

Sites should obtain the 0-hour (pre-dose) PK sample, then instruct the patient to administer study drug. Blood samples for PK analysis should then be drawn at 2 and 4 hours post dose administration.

Week 100 PK

Patients must be instructed to refrain from taking study drug prior to coming to the clinic for the Week 100 visit, as patients will administer study drug in-clinic as instructed by the site. Patients must provide the time and date of the two most recent doses of study drug, prior to the blood samples being collected.

Patients will have blood drawn at a single timepoint (i.e., pre-dose) for PK analysis at this visit.

Sites should obtain the 0-hour (pre-dose) PK sample, then instruct the patient to administer the final dose of study drug in-clinic.

Week 103, Week 104 (B), and Week 108 (B) PK

These PK assessments occur during the Off Treatment Period, so no study drug administration is associated with these assessments.

Patients will have blood drawn at a single timepoint for PK analysis at this visit.

9.10.33. Ambulatory Blood Pressure Monitoring

For adult patients, Ambulatory Blood Pressure Monitoring (ABPM) is an optional sub-study conducted at the timepoints specified in Table 4. To participate, patients must have a baseline ABPM assessment. The baseline assessment must occur during the screening period, ideally 2-3 days prior to Day 1. The additional assessments occur at the following time points: Week 12, Week 48, and between Weeks 88 and 100 (prior to the patient's last dose of study drug), as defined in Table 4.

Participation in the ABPM sub-study is optional; however, patients should be encouraged to participate, and use of home health visits is strongly encouraged to minimize the burden on the patient and to maximize participation.

To ensure a sufficient volume of ABPM data, the Sponsor may halt enrollment of patients not participating in the ABPM sub-study. Participation will be monitored closely as overall enrollment progresses, and the Sponsor will update sites on progress toward achieving sufficient ABPM participation.

A Sponsor-provided device will be placed on the patient by the study team, and the patient must wear the device for approximately 24 hours.

Upon completion of the 24-hour period, the site will collect the device from the patient and ABPM data will be sent to the central vendor to determine if the 24-hour recording passes the validity criteria. The criteria used to define a valid ABPM session for sites to determine the need for a repeat 24-hour session, if possible, are:

- At least 70% of planned inflations are successful during the overall recording session;
- At least 18 hours of analyzable data, and;
- Not more than two consecutive hours of missing data.

For detailed instructions regarding ABPM refer to the study reference manual.

The addition of ABPM to the schedule of assessments occurred through a protocol amendment, and site and patient participation will be offered, once available.

9.10.34 Tanner Staging

Gender appropriate Tanner staging will be performed on all patients who enroll in the study as adolescents. Tanner staging should be performed at Day 1, Week 52 (B), and Week 108 (B), as outlined in Table 4, to monitor and assess sexual maturity. All assessments must be performed even if a patient reaches 18 years of age while participating in the study. Tanner staging may be performed only by a physician (specifically, the principal investigator or sub-investigator). For further guidance and to access the Tanner Staging see the Study Reference Manual.

9.11. Dose Management

DOSE ESCALATION

Both adult and adolescent patients randomized to placebo will remain on placebo throughout the study, undergoing sham titration. Both adult and adolescent patients receiving study drug 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 escalation may need to proceed more slowly if the patient experiences early elevations in ALT/AST over ULN, e.g. at Week 2 (see Section 9.1.2) or if the patient misses visits (see Section during the Dose Escalation Period . 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 1, 2, 4, or 6 with the Medical Monitor. In cases where dose escalation is delayed or not achieved, the investigator should consider dose escalation to goal dose at any time throughout the dosing period.

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

If 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 re-escalation and an unscheduled office visit 2 weeks (± 3 days) after dose re-escalation to perform assessments detailed in Section 9.7.

INTERRUPTION OF STUDY DRUG

In addition to dose de-escalation and re-escalation, the study drug administration can be interrupted, if clinically indicated. The term interruption generally refers to a temporary halt of study drug administration. All efforts should be made to resume study drug at any point during the treatment period following interruption, upon consultation with the Medical Monitor. If there are any questions regarding study drug interruption, please consult the Medical Monitor.

RESUMING STUDY DRUG

Any patient who interrupts study drug for 14 consecutive days or more must have approval from the Medical Monitor prior to resuming study drug.

When a patient resumes study drug, after an extended interruption (e.g., more than 14 days), the site should discuss the appropriate starting dose and visit frequency with the Medical Monitor. The duration of the interruption and the reason for interruption should be taken into consideration when determining how to safely resume study drug. Following an extended interruption, when the investigator deems it is safe for the patient to return to the site for an in-person visit, the investigator should conduct an evaluation to determine whether the patient is still eligible to receive study drug and to determine the appropriate dose, in consultation with the Medical Monitor. This should include a confirmation that the patient's circumstances have not changed in a manner that would prohibit administration of the study drug (e.g., the patient is now taking an excluded medication). Once the investigator determines study drug administration is appropriate, dosing may proceed.

Patients must have a telephone call 1 week after resuming and an unscheduled office visit 2 weeks (± 3 days) after resuming study drug to perform assessments detailed in Section 9.7.

For additional guidance on resuming drug following a positive COVID-19 test, see Section 9.11.5

9.11.1. Dose Escalation Period – Missed In-Person Visits

The first 8 weeks of the trial require intense safety monitoring of patients as they progress through the dose-escalation period of the study. When in-person visits are not be feasible, due to COVID-19 or any other reason, patients who are in the dose escalation period of the study should remain on their current study drug dose. The dose at the last in-person visit, if not the goal dose, will be considered the maximum dose until completion of dose-escalation can be safely resumed (See Section 9.11.5).

Protocol specified in-clinic follow-up visits, for safety/tolerability, must be completed where possible. Required assessments for patients who are unable to have an in-person visit are described in Appendix 2.

9.11.2. Week 8 – 12 Visits – Missed In-Person Visits

Patients in the maintenance period of the trial who have completed dose escalation and who have not reached the Week 12 time point must be assessed at Week 12 by conducting an in-person visit, per protocol. Patients who are unable to return to the clinic/site for a scheduled Week 12 follow-up visit should remain on their current study drug dose and have remote assessments

completed to evaluate assess safety/tolerability. These remote assessments may be conducted as described in Appendix 2.

9.11.3. Post-Week 12 Visits – Missed In-Person Visits

Patients who have completed dose escalation and who have completed the Week 12 Visit must be assessed at their next scheduled visits (as outlined in Table 4). Patients who will be unable to return to the clinic/site for scheduled follow-up visits should remain on their current study drug dose and complete remote assessments to evaluate safety/tolerability until in-clinic visits can be resumed (see Section 9.11.5). These remote assessments may be conducted as described in Appendix 2.

If no in-clinic visit can be completed and remote assessments/laboratory samples cannot be collected within a reasonable time, based on the investigator's discretion, the investigator should consider whether de-escalation may be appropriate.

9.11.4. Dose De-Escalation and Interruption for Missed Safety and Laboratory Assessments

From Protocol Version 7.0 forward, this text was removed, and language was placed within Section 9.11.

9.11.5. Resuming Study Drug After COVID-19 Interruption

Patients who interrupt study drug due to a positive COVID-19 test may resume study drug without an in-clinic visit, at the investigator's discretion, if COVID-19 symptoms are mild, and if the duration of interruption did not exceed 14 days.

Study drug may be resumed when the patient no longer presents an active infection (defined as resolution of symptoms or a negative SARS-CoV-2 test), as assessed by the Investigator and/or the patient's physician(s). If COVID-19 symptoms persist (e.g., loss of taste or smell), the patient should be encouraged to repeat SARS-CoV-2 testing in order to minimize the duration of study drug interruption.

For more information related to study drug management and COVID-19 see Appendix 1, Section 4.5.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

Bardoxolone methyl capsules, 5 mg (size #4), 10 mg (size #2), 15 mg (size #1), and 20 mg (size #0) may be used in this study. The 30 mg dose will be given as two 15 mg capsules. Placebo capsules will have matching capsule sizes to have the same appearance as the active doses.

10.2. Study Drug Packaging and Labeling

The study drug will be supplied as either individual bottles (5, 10, 20 mg dose) or in tamper-evident kits containing two high-density polyethylene (HDPE) bottles (30 mg dose as 2 x 15 mg capsules). 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, 10 mg, 15 mg, or 20 mg strength bardoxolone methyl or the matching placebo capsules. Each bottle will also contain desiccant insert(s) that must not be ingested. Labeling on each kit bottle will contain at minimum the following information:

- Medication ID number;
- Protocol 402-C-1808;
- Caution Statement: New Drug – Limited by Federal Law to Investigational Use. Keep out of reach of children;
- Control or lot number;
- Store at 15° – 25°C (59° – 77°F);
- Reata Pharmaceuticals, Inc., Irving, TX.

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

In the event the investigational product is not packaged as intended or may not adhere to Current Good Manufacturing Practices (CGMP), a complaint should be filed with the Sponsor, ideally through the site's CRA. Guidance on filing study drug complaints is available in the Study Reference Manual, and attention should be given to ensure the patient number is not submitted within the complaint documentation.

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 15° - 25°C (59° - 77°F).

If the investigational product is stored outside of the designated conditions, a temperature excursion notification should be submitted to the Sponsor for review and approval for use of the

affected study drug. Guidance on filing temperature excursions is available in the Study Reference Manual.

10.4. Study Drug Administration

Please refer to Section 9.10.13 for details on study drug administration. It is the responsibility of the investigator or designee to provide clear instructions to the patient regarding the number and type of capsules to be ingested at each study drug administration time point listed in Table 4. Patients must be instructed to continue taking study drug once daily through Week 100 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

Study drug bottles and any unused capsules should be returned to the study staff for eventual disposition by the Sponsor. The investigator or designee will maintain a record of all study drug received, dispensed, and returned. The number of capsules returned at each visit will be recorded by the site for each bottle in the kit. The site will make these records available for Sponsor or designee review.

10.6. Study Drug Handling and Disposal

At any time during the conduct of the study, the Sponsor or its designee will direct the site regarding the final disposition of study drug. No study drug shall be destroyed by the clinical site unless agreed upon in writing by the Sponsor. Documentation of study drug disposition will be retained with the investigator. Refer to the IP Handling Manual for detailed instructions on study drug handling and disposal.

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.

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 it is considered to be study-drug related. Included in this definition are any newly occurring events or previous conditions that have 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 administration of the first dose until the Week 112 (B) study visit as indicated in Table 4) must be reported, regardless of their relationship to study drug or their clinical significance.

For patients who discontinue study drug early (prior to Week 100) and continue to be followed in the study, all AEs should be recorded for 12 weeks following the patient's last dose of study drug. Beyond 12 weeks after the patient's last dose, only those AEs that are relevant to the clinical condition including kidney disease, may have an impact on kidney function, or may impact the interpretation of safety or efficacy data must be reported.

AEs that are related to study procedures should be reported independent of the patient's study drug status or duration since the patient's last dose of study drug. SAEs, if considered related to study drug, can be reported at any time during the study duration.

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 Week 112 (B) study visit indicated in Table 4, as appropriate). Certain pregnancy outcomes will require submission as an SAE (see Section 9.8).

The investigator is responsible for reporting to Reata or designee all AEs and SAEs that are observed or reported by the patient during the study (from the time of administration of the first dose of study drug until the Week 112 (B) study visit indicated in Table 4), including events resulting from protocol-associated procedures as defined in relevant legislation, and regardless of their relationship to study drug or their clinical significance. For patients who discontinue study drug early, SAEs should be reported through 12 weeks following the date of last dose of study drug. SAEs, if considered related to study drug, should be reported at any time during the study. 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.

For information on ESKD related SAEs see section 9.1.9.

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.

For regulatory reporting purposes, an adverse event is considered to be related when the causality evaluation is either "Definitely Related, Probably Related, or Possibly Related." An adverse event is considered to be not related when the causality evaluation is either "Unlikely Related or Not Related."

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 the Week 112 (B) study visit, as indicated in Table 4, regardless of their relationship to study drug or their clinical significance. For patients who discontinue study drug early (prior to Week 100) and continue to be followed in the study, all AEs should be recorded for 12 weeks following the patient's last dose of study drug. Beyond 12 weeks after the patient's last dose, only those AEs that are relevant to the clinical condition including kidney disease, may have an impact on kidney function, or may impact the interpretation of safety or efficacy data must be reported.

AEs that are related to study procedures should be reported independent of the patient's study drug status or duration since the patient's last dose of 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.

For guidance on how to handle AEs that change in severity (e.g., worsening or improving), see the eCRF Completion Guidelines. All drug-related (possibly, probably, or definitely related, see Section 11.4) AEs and clinically significant abnormal laboratory test results reported or observed during the study must be followed to resolution (either return to baseline, within normal limits, or stabilization). All non-drug related AEs or clinically significant abnormal laboratory test results will be followed through the Week 112 (B) study visit or for 12 weeks following the last dose for patients who discontinue study drug early.

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

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

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

11.7. Reporting Serious Adverse Events

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

To report the SAE, fax or email the completed SAE form [redacted] within 24 hours of awareness.

[redacted]

[redacted]: [redacted]

E-mail: [redacted]

For questions regarding SAE reporting, contact your study manager, medical monitor, [redacted].

Follow-Up Reports

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

Within 24 hours of receipt of new information, the updated follow-up SAE form, along with any supporting documentation (e.g., patient discharge summary or autopsy reports), should be faxed or emailed [redacted].

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 SAEs which are commonly observed in this patient population as part of CKD progression will not be reported to regulatory authorities as individual expedited reports, except in unusual circumstances:

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

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

12. STATISTICS

12.1. Sample Size

With 850 patients enrolled, the study will have approximately 80% power to detect a difference between the two treatment groups in change from baseline eGFR of 2.3 mL/min/1.73 m^2. The power calculation was based on a 2-sample t-test as an estimate for the planned ANCOVA analysis and assumes the following:

- Overall two-sided Type I error rate total of 0.05;
- Standard deviation of change from baseline in eGFR of 12 mL/min/1.73 m^2;
- Analyses are based on the intent-to-treat (ITT) population;
- Missing data will be imputed using multiple imputation.

ANCOVA analysis is expected to have approximately the same power as the t-test used for study planning. The method for maintaining strict control of the Type I error for the trial will be described in the statistical analysis plan (SAP). Appropriate sensitivity analyses of the primary analysis will be specified in the SAP.

12.2. Study Variables

12.2.1. Pharmacokinetic Variables

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

12.2.2. Efficacy Variables

Change from baseline in eGFR will be used to determine the primary, secondary, [redacted] endpoints. [redacted]

12.2.3. Safety Variables

The safety variables include results of laboratory testing, vital sign measurements, ECG results, height, weight, [redacted], 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 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. Analysis of Efficacy

The ITT population, which includes all patients randomized within each cohort, will be used as the population for assessment of the efficacy endpoints. This includes patients on tolvaptan who have already enrolled under Version 2 of the protocol.

Analysis of covariance (ANCOVA) will be used to analyze the primary efficacy endpoints of change from baseline in off-treatment eGFR. The model will include change from baseline in eGFR as the dependent variable, treatment group as fixed effect, and baseline eGFR as a continuous covariate. Other covariates may be specified in the SAP. The off-treatment endpoints assess the preserved drug benefit relative to placebo following withdrawal of treatment; therefore, analyses of these endpoints do not include eGFR values collected during treatment. Sensitivity analyses, including a tipping point analysis, will be performed to assess the impact of missing data.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

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

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

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

In case that study sites are closed for any visitors and monitors over a certain period of time during the COVID-19 pandemic, a risk-based approach to monitoring will be taken, focusing on certain sites, certain data points and certain processes that are critical to ensure the rights, safety and well-being of trial participants and the integrity of the trial (and trial data). The results of adjusted monitoring/review measures and their impact will be reported to the Sponsor in monitoring reports and in the clinical study report, where applicable. Adjusting monitoring activities may include a combination of on-site and off-site monitoring, where permitted by local regulations. Remote source data verification may also be taken into consideration, where permitted by local regulations.

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/study drug storage facilities.

14.2. Financial Disclosure

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

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

14.3. Sponsor Obligations

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

14.4. Investigator Documentation

Before beginning the study, the principal investigator will be asked to comply with ICH E6(R2) 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 (and assent, if applicable), 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 or equivalent statement of investigator, 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 (and assent, if applicable) 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 (and assent, if appliable) 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 Council for Harmonisation for Technical Requirements for Pharmaceuticals for Human Use (ICH) for Guidance for Industry on Good Clinical Practice (GCP) ICH E6(R2) [https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf] and the principles of the Declaration of Helsinki [https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/]. The principal investigator must conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

15.3. Written Informed Consent

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

Before enrollment, each prospective patient will be given a full explanation of the study and be allowed to read the approved informed consent form. Once the principal investigator or designee is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing the informed consent form.

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

For adolescent patients, informed consent will be obtained from the parent(s) or legal guardian in accordance with regional laws or regulations. In addition, dependent upon the patient's age and IRBs, IEC, and/or local legal requirements, assent of the patient must also be obtained. Adolescent patients may be asked to personally sign and date either a separately designed, written assent form, or the written informed consent.

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 site personnel and the responsible monitor during monitoring visits, and those observations will be communicated to the investigator. Protocol deviations will be reviewed and any that are a serious breach of GCP and/or the protocol will be reported to the relevant regulatory agency, as required. Protocol waivers are not allowed for sites in the United Kingdom, and protocol waivers will not be granted by the Sponsor in any participating countries.

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.

Deviations will be reported, evaluated, and discussed according to the Protocol Deviation Plan and in the final study report.

All protocol deviations due to the impacts of COVID-19 will be identified and documented accordingly by the site and the Sponsor. When visits are completed remotely (due to COVID-19 or other reasons), sites should ensure the completion of at least those assessments listed in APPENDIX 2. Where these study procedures are completed remotely, any additional study procedures that cannot be completed will be noted as missing and will not be considered as a protocol deviation. The failure to complete the minimally required procedures outlined in 0, will be considered a protocol 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, or for the duration required by local regulations, whichever is longer. If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

16.2. Case Report Forms

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

17. PUBLICATION POLICY

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

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

18. REFERENCES

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APPENDIX 1. COVID-19 MITIGATIONS

This appendix outlines the mitigation strategies adopted to protect the health of participants in the study, while maintaining compliance with good clinical practice (GCP) and minimizing the risk to trial integrity during the COVID-19 (Coronavirus Disease 2019) pandemic.

The mitigations will be in place as long as COVID-19 has an impact on trial conduct.

All measures/mitigations undertaken will be done in accordance with the applicable regional and national guidelines of the health authorities (for example, the Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic by the European Medicines Agency [EMA] and the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency).

COVID-19 impacts to the conduct of study assessments and data collection are noted within the clinical database.

1. SITE OPERATIONS & PATIENT MANAGEMENT

If study sites close or restrict access to study teams during the COVID-19 pandemic, study teams must maintain open lines of communication with active study participants. Additionally, the Sponsor is to be regularly updated on changes to the site's status regarding closures, access limitations, contact information or other important information. Sites are encouraged to provide alternate contact information to their patients and the Sponsor. Updates may be sent to the Sponsor study team (COVID19@reatapharma.com).

2. COVID-19 INFECTED PATIENTS AND STUDY DRUG USE

If a patient enrolled in the study tests positive for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), study drug must be temporarily discontinued. The Sponsor must be notified immediately for additional guidance.

Study drug may be resumed when the patient no longer presents an active infection (defined as resolution of symptoms or a negative SARS-CoV-2 test), as assessed by the Investigator and/or the patient's physician(s). If COVID-19 symptoms persist (e.g., loss of taste or smell), the patient should be encouraged to repeat SARS-CoV-2 testing in order to minimize the duration of study drug interruption.

Patients who interrupt study drug due to a positive COVID-19 test may resume study drug without an in-clinic visit, at the investigator's discretion, if COVID-19 symptoms are mild, and if the duration of interruption did not exceed 14 days.

The maximum duration of treatment interruption due to COVID-19 infection must be determined based on the patient's symptoms and the investigator's discretion. Instructions for how to resume study drug (i.e., appropriate dose for restarting and appropriate visit schedule) are contained in Section 9.11.

Additional instructions on resuming study drug are provided in Section 9.11.5

3. STUDY DRUG ACCESS

In order to maintain dosing continuity during the COVID-19 pandemic, study drug may be shipped from the sites to patients using couriered tracking services, when a patient is not able or willing to travel to the study site. Drug will not be shipped directly from the Sponsor to patients. Stability information for study drug shipments is contained in the "Guidance for Direct-to-Patient Shipping of RTA-402 Drug Product Capsules during the Coronavirus (COVID-19) Pandemic" (Attachment 1). For shipments anticipated to exceed a 48-hour transit time, sites will be supplied with temperature monitors upon request. When a shipment exceeds this transit time, the Sponsor should be notified immediately via the COVID-19 Investigational Product Temperature Excursion form. The Sponsor will assess whether the product is fit for use. During this assessment period, the patient should be informed to not take the study drug until further notice from the site. Study drug dispensation should be recorded in the appropriate drug accountability logs and all study drug receipts of delivery should be filed in the Investigative Site File.

4. DOSE MANAGEMENT

4.1 Dose Escalation Period

Refer to Section 9.11.1.

4.2 Week 8-12 Visits

Refer to Section 9.11.2

4.3 Post-Week 12 Visits

Refer to Section 9.11.3

4.4 Dose De-escalation and Interruption for Missed Safety and Laboratory Assessments

Refer to Section 9.11.4.

4.5 Resuming or Dose-escalating Study Drug after Interruptions or Changes

Refer to Section 9.11.5.

5. DEVIATIONS

Refer to Section 15.6.

6. MONITORING

Refer to Section 13.1.

APPENDIX 2. USE OF HOME HEALTHCARE

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

Visits conducted over the phone (or via telemedicine, if available), at a minimum should include the following assessments:

- Adverse-event assessment
- Prior and concomitant medication assessment

In-home visits at a minimum should include the following assessments:

- Safety labs (may also be done by local laboratories)
  - Clinical chemistry (including eGFR)
  - BNP and NT-proBNP
  - Hematology
  - Urinalysis and microscopy / Urine collection for ACR
  - Urine pregnancy test for WOCBP
- Vital signs
- Weight at home
- Adverse event assessment
- Prior and concomitant medication assessment
- Height

ATTACHMENT 1: GUIDANCE FOR DIRECT-TO-PATIENT SHIPPING OF RTA-402 DRUG PRODUCT CAPSULES DURING THE CORONAVIRUS (COVID-19) PANDEMIC

March 25, 2020

To: Clinical Program Operations
Reata Pharmaceuticals, Inc.

From: Chemistry, Manufacturing & Controls / Quality Assurance
Reata Pharmaceuticals, Inc.

Via E-mail Transmission

RE: Guidance for Direct-to-Patient Shipping of RTA 402 Drug Product Capsules during the Coronavirus (COVID-19) Pandemic

As a result of the coronavirus (COVID-19), certain adjustments have been made to ensure study patients receive their investigational product, on time, and consistently.

For clinical investigators, where patients are unable to travel outside of their home to the site, one adjustment being implemented is the shipping of investigational product directly to the patient, from the clinical investigator site.

As background, RTA 402 drug product capsule kits (30ct, 1g desiccant, 60 mL bottle) have been assessed for stability following ICH guidelines for long term and accelerated conditions. The results support the current labeled storage conditions of controlled room temperature, which is defined as 20°C to 25°C (68°F to 77°F), with brief excursions allowed to 15°C to 30°C (59°F to 86°F).

The stability results also provide supporting data to assess potential impact of short-term temperature excursions outside the labeled storage conditions. More specifically, for drug product capsule stored as a 30ct supply in 60 ml bottle with 1g desiccant, no significant changes in drug product quality were observed for 6 months for accelerated (40°C/75% RH) and 36 months for long term (25°C/60%RH) conditions.

Given the stability of the product under multiple temperatures and relative humidity conditions, it can be concluded that short term temperature excursions above 30°C and low as 15°C during storage are acceptable. For those excursions to non-freezing temperatures below 15°C but at or above 1°C, no additional risk to drug product quality is presented based on the well-established principal of Arrhenius degradation kinetics (i.e., degradation reaction rates are temperature-dependent and occur faster at higher temperatures and slower at lower temperatures).

In consideration of the product stability information, the following direct-to-patient guidance is provided during this coronavirus (COVID-19) pandemic period:

1. To mitigate any unforeseen issues impacting the shipment (i.e., lengthy delays, extreme temperatures, etc.), shipping only the minimum number of product required for patient dosing administration and priority overnight shipment is advised.

2. While the data provides assurance that RTA 402 Drug Product Capsules are stable, additional shipping and storage studies are either planned or currently being conducted. As such, certain limitations have been placed on the product until these results are reported. Accordingly, shipment durations during this period lasting longer than 48 hours, without a temperature monitor, are not advised. If shipment exceeds this duration due to unforeseen shipping delays, the site should contact Reata for further guidance.

Additional guidance will be provided when data is available.

Best regards,

[redacted]

3/25/2020 | 1:00:21 PM CDT

[redacted]

[redacted]

3/25/2020 | 1:38:03 PM CDT

[redacted]

AMENDMENT CHANGE SUMMARY DOCUMENT

CLINICAL STUDY PROTOCOL 402-C-1808

Study Title: A Phase 3 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with Autosomal Dominant Polycystic Kidney Disease (FALCON)

Protocol History

Version 7.0 – 25 May 2022
Version 6.0 – 04 February 2022
Version 5.1 Czech Republic – 30 March 2021
Version 5.1 United Kingdom – 30 March 2021
Version 5.1 Germany – 30 March 2021
Version 5.0 – 25 February 2021
Version 4.1 Czech Republic – 28 August 2020
Version 4.1 United Kingdom – 25 June 2020
Version 4.1 Germany – 25 June 2020
Version 4.0 – 25 June 2020
Version 3.1 United Kingdom – 09 January 2020
Version 3.1 Germany – 19 December 2019
Version 3.1 Czech Republic – 18 November 2019
Version 3.0 – 16 July 2019
Version 2.0 – 04 March 2019
Version 1.0 – 12 December 2018

CONFIDENTIALITY STATEMENT

SUMMARY OF CHANGES

The following document outlines the changes made to Version 6 to produce the text of Version 7. Additionally, the following points are provided:

- New text added is underscored; deleted text is designated by ~~strikethrough~~.
- The changes made in the body of the protocol are reflected in the synopsis; the corresponding changes made in the synopsis are not described.
- Grammatical corrections and minor editorial changes are not described.
- Section numbers refer to the numbers in the new version of the protocol.

Section	Version 7	Rationale
Title Page	Version ~~6~~7.0 – ~~04 FEBRUARY~~25 MAY 2022 **Protocol Version History** Version 6.0 – 04 February 2022 Version 5.1 Czech Republic – 30 March 2021 Version 5.1 United Kingdom – 30 March 2021 Version 5.1 Germany – 30 March 2021 Version 5.0 – 25 February 2021 Version 4.1 Czech Republic – 28 August 2020 Version 4.1 United Kingdom – 25 June 2020 Version 4.1 Germany – 25 June 2020 Version 4.0 – 25 June 2020 Version 3.1 United Kingdom – 09 January 2020 Version 3.1 Germany – ~~19~~02 December 2019	Updated to reflect current version of the Protocol and added country specific version of the protocol that have been incorporated.
2. Synopsis: Studied Period	Estimated date last patient completed: ~~April~~ November 2025	Updated to reflect new enrollment projection.
[redacted]	[redacted]	Updated to match the body of the protocol.
2. Synopsis: Methodology	These modifications are described in Appendix 1 (COVID-19 Mitigations~~).~~), Appendix 2 (Use of Home Healthcare) and throughout the protocol	Updated to specify COVID-19 modifications are not only found in Appendix 1, but also in the newly added Appendix 2 and throughout the protocol.

2. Synopsis: Diagnosis and main criteria for inclusion	10. Patients receiving an SGLT2 inhibitor must be on a stable dose for at least 4 weeks prior to the Screen A visit	Added language, since SGLT2 inhibitors are used in treatment of CKD and will have direct impact on eGFR. It is important to have subject on a stable dose prior and during the study.
6.2.4. 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.~~ pediatric growth (height and weight), and sexual maturity using Tanner staging.	Added based on health authority feedback seeking confirmation of adequate measures to monitor safety of, and minimize risk to, the adolescent population in the study.
7.3.2. Dose Escalation Plan	~~Patients~~ Both adult and adolescent patients randomized to placebo will remain on placebo throughout the study, undergoing sham titration. ~~Patients~~ Both adult and adolescent patients receiving bardoxolone methyl will start with once-daily dosing at 5 mg and will dose-escalate to 10 mg at Week 2, to 20 mg at Week 4, and then to 30 mg at Week 6 (only if baseline ACR > 300 mg/g) unless contraindicated clinically and approved by the Medical Monitor. ~~Dose escalation may need to proceed more slowly if the patient experiences early elevations in ALT/AST over ULN, e.g. at Week 2 (see Section 9.1.2). The dosing objective is to titrate patients to the maximum 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 1, 2, 4, or 6 with the Medical Monitor. In cases where dose escalation is delayed or not achieved, the investigator should consider dose escalation to goal dose at any time throughout the dosing period~~	Clarification added to specify both adults and adolescents will follow the same dose escalation plan. Relocated and consolidated all dose management text to Section 9.11 (Dose Management).
7.3.3 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 the dose and must be documented. After dose de-escalation, patients must return for an unscheduled office visit within 4 weeks (± 3 days) to perform the assessments detailed in Section 9.7.~~	Relocated and consolidated all dose management text to Section 9.11 (Dose Management).

	~~If 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 re-escalation and an unscheduled office visit 2 weeks (± 3 days) after dose re-escalation to perform assessments detailed in Section 9.7.~~ For detailed instructions on dose management, refer to Section 9.11.	
7.3.4. Dose Interruption and Re-Challenge/ Re-Initiation	~~In addition to dose de-escalation and re-escalation, the study drug administration can be interrupted, if clinically indicated. The term interruption generally refers to a temporary halt of study drug administration. All efforts should be made to re-challenge the study drug at any point during the treatment period following interruption, upon consultation with the Medical Monitor. If there are any questions regarding study drug interruption, please consult the Medical Monitor.~~ ~~When a patient resumes or re-challenges study drug, after an extended interruption (e.g., more than several weeks), the site should discuss the appropriate starting dose and visit frequency with the Medical Monitor. The duration of the interruption and the reason for interruption should be taken into consideration when determining how to safely resume or re-challenge study drug.~~ For detailed instructions on dose management, refer to Section 9.11.	Relocated and consolidated all dose management text to Section 9.11 (Dose Management).
7.5. Schedule of Assessments Table 4: Schedule of Assessments	Week 5 (Phone) Day 38 ±~~3~~2 Days	Visit window inadvertently changed to ±3 Days between protocol V5.0 to V6.0. Corrected back to ±2 Days.
7.5. Schedule of Assessments Table 4: Schedule of Assessments	Tanner Staging: Day 1, Week 52(B), Week 108(B)	Added new Tanner Staging Assessment at specific timepoints to monitor the growth and sexual development of adolescents.
7.5. Schedule of Assessments Table 4: Schedule of Assessments	[d] Screening eligibility procedures do not need to be repeated on Day 1; however, a review of any changes in eligibility criteria should be evaluated prior to Day 1 procedures~~, and a urine pregnancy test should be performed for WOCBP~~	Pregnancy tests are required at all visits, as outlined in Table 4. Language was removed to avoid potential confusion due to use of the word "should."

7.5. Schedule of Assessments Table 4: Schedule of Assessments	[e] ~~All patients' height~~ Height will be recorded in centimeters. Adult patients (18 ≤ age ≤ 70 years at Screen A visit) will be measured at Screen A only. Adolescent patients (12 ≤ age < 18 years at Screen A visit) will be measured at all specified timepoints.	Minor correction
7.5. Schedule of Assessments Table 4: Schedule of Assessments	[k] eGFR will be calculated and appear on lab reports for Screen A and Screen B visits, eGFR will no longer be calculated for any visits after the Screening period.	The central laboratory will no longer be calculating and reporting eGFR values on patient lab reports outside of the Screening period.
[redacted]	[redacted]	[redacted]
7.5. Schedule of Assessments Table 4: Schedule of Assessments	[o] Ambulatory Blood Pressure Monitoring (ABPM) is an optional sub-study for adult patients (18 ≤ age ≤ 70 years at Screen A) who enroll under protocol version 6.0 (or greater) and consent to the procedure prior to randomization. See Section 9.10.33 for details and timing on ABPM. ABPM will not be performed on adolescent patients (12 ≤ age < 18 years at ~~Screen A).~~ randomization).	Clarification that ABPM sub-study may only enroll adult patients.
7.5. Schedule of Assessments Table 4: Schedule of Assessments	[q] Adolescent patients (12 ≤ age < 18 years at Screen A visit) will be assessed by Tanner staging at all specified timepoints.	Clarification that Tanner Staging pertains only to adolescent patients.
7.5. Schedule of Assessments Table 4: Schedule of Assessments	[t] Unless permitted in the protocol, all study activities, including assessments and sample collection, are expected to be completed on the same day (i.e., day of the visit).	Clarification that all study procedures be performed the day of the visit.
8.1 Patient Inclusion Criteria	NOTE: Participating sites in Australia will only treat adult patients, defined as 18 years old or older at the time of consent.	Country specific clarification added, as sites in Australia will not enroll adolescent patients.

8.1 Patient Inclusion Criteria	3. eGFR must: a. Have a percent difference ≤ 25% at screening (the values at Screen A and Screen B), and; b. Have an average (the values at Screen A and Screen B) ≥ 30 to ≤ 90 mL/min/1.73 m2 for patients 12 55 years or ≥ 30 to ≤ 44 mL/min/1.73 m2 for patients 56 to 70 years, and; c. Support ADPKD disease progression (i.e., average yearly eGFR decline of ≥ 2.0 mL/min/1.73 m2 for ~~2 consecutive~~ the past two years) for patients with either screening eGFR ≥ 60 to ≤ 90 mL/min/1.73 m2 or age 56 to 70 years (See Protocol Section 9.10.2)	Clarification that disease progression is assessed based on the past two years.
8.1 Patient Inclusion Criteria	10. Patients receiving an SGLT2 inhibitor must be on a stable dose for at least 4 weeks prior to the Screen A visit;	Added language, since SGLT2 inhibitors are used in treatment of CKD and will have direct impact on eGFR. It is important to have subject on a stable dose prior and during the study.
8.3.1. Screening Period	The screening period begins with the signing of the informed consent/assent form at the Screen A visit and ends at the start of the Day 1 visit. Where the signing of the informed consent/assent precedes the Screen A visit, the screening period is considered to begin at the Screen A visit. The duration of the screening period must not exceed 90 days. The Screen A procedures may be completed across multiple days. Efforts should be made to ensure the Screen B visit is no more than 30 days prior to Day 1. Sites must not initiate screening of an adolescent who will become an adult prior to Day 1. If, ~~at the time of~~ prior to randomization, ~~a~~ an adolescent patient ~~is~~ who screened has become an adult, the patient must be screen-failed and rescreened, such that eligibility ~~must be~~ is assessed based on the adult eligibility parameters (ADPKD diagnosis and eGFR calculation).	Clarified that the Screening period begins at the Screen A visit, even when the ICF is signed prior. Refined instructions to sites regarding patients who transition from adolescent to adult during screening.
8.3.3. Off-Treatment Period	AEs should be reported ~~for 30 days following~~ until the ~~patient's last dose of~~ Week 112 (B) study ~~drug~~ visit.	Because endpoint data are being collected through 12 weeks following the last dose of drug, the AE collection period was extended.
8.5. Patient Discontinuation and Termination	The reason for a patient's discontinuation from study drug or study termination will be recorded in the electronic case report form (eCRF). Any patient who ~~discontinues~~ interrupts study drug for 14 consecutive days or more must have approval from the Medical Monitor prior to resuming ~~treatment with~~ study drug.	Basic clarification

8.5.1. Study Drug Discontinuation Criteria	For patients who discontinue treatment prior to Week 100, see Section 8.3.3 for the required off-treatment assessments. After the off-treatment assessments, the patient will continue with follow-up assessments through Week 112. The collection of laboratory data and vital status through Week 112 (B) is important for trial integrity, and data may be obtained through in-person clinic visits or through home health visits. See Section 9.10.16 for Adverse Event Collection following study drug discontinuation.	Added language to emphasize the importance of continuing follow up through Week 112 for patients who discontinue drug early.
9.1.2. Management of Elevated Transaminase Levels (ALT and/ or AST)	Patients ~~restarting~~ who meet the interruption criteria outlined above must restart study drug should start at the 5 mg dose level and dose titrate according to Section 7.3.3. ~~The hepatobiliary tree must be assessed by ultrasound or magnetic resonance imaging (MRI) for patients who meet temporary discontinuation criteria. Based on imaging results, if additional tests/studies are warranted, this should be discussed with the Medical Monitor.~~	Clarified that 5mg restarting dose must be used when interruption criteria are met. Removed redundant instruction regarding visualization of hepatobiliary tree.
9.1.4. Weight Loss	Adults - The investigator should evaluate a patient for unexplained weight loss of 7% or greater from the Day 1 weight. Ongoing assessments of other symptomology (for example: nausea, vomiting, abdominal pain or poor appetite) may be warranted to ensure the patient is receiving adequate nutrition and ~~consideration of~~ evaluate for other ~~etiologies~~ causes of weight loss ~~may be warranted for patients receiving bardoxolone methyl.~~ Adolescents - If weight loss of greater than 5% from the Day 1 weight is observed, the investigator should temporarily stop study drug, and evaluate the patient for any symptomology (for example: nausea, vomiting, abdominal pain or poor appetite) leading to weight loss, and/or other causes of weight loss. The investigator should inform the Medical Monitor prior to stopping study drug, and the investigator and Medical Monitor should discuss management of the patient.	Language was added to clarify assessment of symptomology related to weight loss and specify criteria for interruption of IP in adolescents with a >5% drop in weight from the Day 1 measurement.
9.1.9. End Stage Kidney Disease	For patients with eGFR ≤ 15.0 mL/min/1.73 m2, (as calculated by the site, using the central lab-provided serum creatinine and the formulas provided in Section 9.10.18.1), initiate more frequent follow-up to closely monitor safety assessments (i.e., clinical chemistry (incl. eGFR), hematology, vital sign assessments (incl. weight), BNP and NT-proBNP).	Language added to guide sites on how eGFR should be calculated in the absence of values being present on lab reports.
9.1.10. Monitoring Growth and Sexual Development in Adolescents	Growth and sexual development will be assessed through an evaluation of height, weight, and Tanner Staging. See the Study Reference Manual for details on the Tanner staging. Body weight should be measured daily by patients/caregivers using a provided weighing scale. Weight and height will also be measured at all site visits, as outlined in Section 9.10.7. Patients should be instructed to inform the site if there is an observed weight loss of more than 3 pounds (1.4kg) in between clinic visits (Section 9.1.1).	Added based on health authority feedback seeking confirmation of adequate measures to monitor safety of, and minimize risk to, the adolescent population in

	The Medical Monitor will routinely evaluate both weight and height entered into the clinical database of adolescents and will inform the investigator to initiate further evaluation if there is a weight loss of ≥5% or lack of expected growth per growth charts. Sexual maturity will be assessed by the investigator using Tanner Staging. If any abnormal patterns of sexual maturity are identified on evaluation of Tanner Staging, the Medical Monitor should be notified for additional discussion.	the study.
9.3.1.2. Prohibited Medications	~~Chronic~~Concomitant use with chronic (> 2 weeks) immunosuppressive therapy~~, or need for~~ (corticosteroids, including therapies such as glucocorticoids, oncologic preparations, and anti-TNFα agents [e.g., infliximab (Remicade®), adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®)~~] within 12 weeks prior to randomization. Glucocorticoid intra-articular injections, inhaled products, topical preparations, and nasal preparations are allowed.®)])~~ is prohibited. ~~Patients who~~ Concomitant use with tolvaptan, somatostatin analogues, and any other investigational drug or device is prohibited. Concomitant dosing with prohibited medications is not allowed and will not be approved by the Medical Monitor. If a site becomes aware of a patient administering a prohibited medication, the Medical Monitor should be notified immediately to determine whether study drug should be permanently discontinued or whether an interruption is appropriate. To minimize missing data and to maintain study integrity, patients who must take prohibited medications during the study should~~ not discontinue study drug solely on this basis~~. ~~Consultation with the Medical Monitor should occur prior to~~ Continue follow-up visits, even after study drug discontinuation,~~ or withdrawing a patient ,~~ unless directed otherwise by the Medical Monitor. Certain prohibited medications (e.g., tolvaptan) will warrant termination from the study, due to the potential for the concomitant medication to confound the interpretation of study data. Sites must avoid initiation of prohibited medications until all Off-Treatment assessments are completed (approximately 12 weeks following the patient's last dose of study drug). If a patient permanently discontinues study drug and continues being followed in the study, the administration of a prohibited medication is no longer considered a protocol deviation after 12 weeks following the patient's last dose of study drug. Beginning 12 weeks after the patient's last dose, administration of a prohibited medication does not require input from the Medical Monitor. Importantly, the administration of any medications listed in this section should be recorded in the concomitant medication page of the EDC independent of the patient's study drug status or duration since the patient's last dose of study drug, in order to ensure accurate interpretation of safety and efficacy data.	Added language and additional instruction on how to handle administration of prohibited medications in patients who have stopped study drug, and who continue to be followed in the trial. Added requirement for Medical Monitor input when a prohibited medication is used or is anticipated. Use of tolvaptan in a patient who has stopped study drug will warrant termination from the study, due to confounding effects on data interpretation.
9.3.2. Permitted Medications	Allowed concomitant medications include the following: • Antibiotics, including (but not limited to) fluoroquinolones and trimethoprim-sulfamethoxazole (if the antibiotic being prescribed is a moderate or strong CYP3A4 inhibitor or inducer, see Section 9.3.1.2~~9.3.10~~); • Daily multivitamins or recommended daily supplements; • Other medications intended to manage concurrent diseases, as authorized by the treating physician;	Country specific language was inadvertently removed between protocol V5.0 to V6.0. Language has been added to V7.

	• Statins (e.g., pravastatin or rosuvastatin), in the Czech Republic and globally; • Pain management: acetaminophen, and other adjuvant analgesics and opioids may be used as deemed appropriate by the investigator, in the Czech Republic and globally; • Oral, implantable, or injectable contraceptives; • Glucocorticoid intra-articular injections, inhaled products, topical preparations, and nasal preparations.	
9.3.2. Permitted Medications	Patients taking medication chronically, including ACE inhibitors ~~and~~, ARBs, and SGLT2 inhibitors 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.	Updated to reference SLGT2i
9.4. Treatment Compliance	A lack of treatment compliance during any evaluation period (visit to visit) should be entered as a protocol deviation. Patients should record in the patient diary all administered and missed doses of study drug. The reason for a missed dose should be recorded in the patient diary. ~~A missed~~ Missing dose includes ~~drug holidays and temporary~~ inadvertent missed doses as well as study drug interruptions and discontinuations. Patients will be asked to return all unused study drug (study drug bottles and any unused capsules). The study drug must not be used for reasons other than that described in the protocol.	Language added to define "missed doses" to minimize ambiguity in interpretation
9.7. Unscheduled Visits	Unscheduled visits conducted for the following reasons should include collection of AEs, clinical chemistry, BNP/NT-proBNP, hematology, concomitant medication collection, and vital signs: • Resuming study drug following an extended interruption;	Clarified that unscheduled visits may be conducted to resume study drug following an interruption
9.8.1. Women of Childbearing Potential and Fertile Males	Czech Republic Only: Women of childbearing potential (WOCBP) are those who have experienced menarche and are not surgically sterile (no history of bilateral tubal ligation, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), and are not postmenopausal (defined as no menses for at least 1 year without an alternative medical cause). Fertile males are those who have entered puberty or reached physical maturation (after puberty) and are not surgically sterile (no history of bilateral orchiectomy)	Country specific language was inadvertently excluded. Language has been added to V7.
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)) Double-barrier methods are not allowed for patients at participating sites in Germany and Australia;	Country specific language was inadvertently excluded. Language has been added to V7.

9.8.2. Methods of Birth Control	During Screening, while taking study drug and until 30 days after the final dose of study medication is taken, fertile males who have female partners of childbearing potential must practice one of the following methods of birth control: • Use double barrier contraception method, defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream, diaphragm (always use with spermicidal jelly/cream)). Double-barrier method is not allowed for patients at participating sites in Germany and Australia: • Have had a vasectomy (with vasectomy performed at least 6 months prior to screening with the appropriate post-procedure documentation of surgical success) (not permitted in the United Kingdom) • Partner contraception methods; must be the sole partner for that patient: – Use of an intrauterine device; – Use of hormonal contraceptives (oral, parenteral, intravaginal or transdermal) for at least 60 days prior to start of study drug administration; – Surgically sterile partner (bilateral tubal ligation, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy); fallopian inserts with confirmed blockage (e.g., x-ray, ultrasound) (not permitted in the Czech Republic); – Reproductive potential has been terminated by radiation (not permitted in the Czech Republic);	Country specific language was inadvertently excluded. Language has been added to V7.
9.10.2. Inclusion/ Exclusion	Inclusion 3c must show disease progression using average yearly eGFR decline of ≥ 2.0 mL/min/1.73 m2 from the ~~last~~ past two ~~consecutive~~ years. If a patient has limited historical eGFR values from the past two years, the investigator must discuss the patient's eligibility with the Medical Monitor.	Clarification that disease progression is assessed based on the past two years.
9.10.4. Prior and Current Concomitant Medications	All medications will be recorded through the Week 112 visit as indicated in Table 4. For patients who remain on study drug, the administration of any medications should be recorded in the concomitant medication page of the EDC through Week 112, For patients who discontinue study drug early and continue to be followed in the study, all concomitant medications should be recorded for 12 weeks following the patient's last dose of study drug. Beyond 12 weeks after the patient's last dose, only those medications that are relevant to the clinical condition including kidney disease or that may have a potential impact on kidney function must be recorded in the concomitant medication page of the EDC. Unscheduled phone visits may be used, as necessary, to ensure accurate collection of concomitant medications of interest.	Language revised to ensure consistent data collection related to concomitant medication and prohibited medication use to aid in safety data review and efficacy analysis.

	Importantly, the administration of any medications listed in Section 9.3.1.2 (Prohibited Medications) should be recorded in the concomitant medication page of the EDC independent of the patient's study drug status or duration since the patient's last dose of study drug, in order to ensure accurate interpretation of safety and efficacy data.	
9.10.6. Height	Height should be measured without footwear or prosthetics using a wall-mounted stadiometer if performed in-clinic. For adult patients (18 ≤ age ≤ 70 years at Screen A visit), height is measured at Screen A. Adolescent patients (12 ≤ age < 18 years at Screen A visit), height is measured at the timepoints specified in Table 4, when in clinic visits are not possible, home health nurses should be used (see Appendix 2).	Language added to define timing and methods of height collection.
9.10.7. Weight and Body Mass Index (BMI)	In the event the Sponsor-provided scale is temporarily unavailable (e.g., patient is traveling, replacement scale has not arrived to patient, etc.), patients may use any available scale. Missing more than 20% of expected weight records in the patient diary during any evaluation period (visit to visit) is considered as non-compliance, which should be reported as a deviation.	Language added to define what will be considered as subject non-compliance regarding missed at home weights.
9.10.11. Comprehensive Physical Examination & Targeted Physical Examination	~~A comprehensive physical examination~~ Physical examinations must be performed by a physician, physician assistant, or registered nurse practitioner. A comprehensive physical examination must be performed as indicated in Table 4 and as documented within the medical record. Table 4. If the investigator observes no symptoms that warrant further examination, the investigator may forego a more detailed physical examination, and the targeted physical examination may be considered complete.	Clarification added to ensure targeted physical exams are performed, as indicated in Table 4, and more detailed physical exams are conducted when needed.
9.10.13 Study Drug Administration	Refer to Section 9.4 and 9.11 for treatment compliance and detail in dose management.	Language added to guide sites to the treatment compliance and dose management sections.
9.10.16. Adverse Event Collection	AEs should be reported from the time of the first dose until the Week 112 (B) visit as indicated in Table 4. For patients who discontinue study drug early (prior to Week 100) and continue to be followed in the study, all AEs should be recorded for 12 weeks following the patient's last dose of study drug. Beyond 12 weeks after the patient's last dose, only those AEs that are relevant to the clinical condition including kidney disease, may have an impact on kidney function, or may impact the interpretation of safety or efficacy data must be recorded in the AE log within the EDC. Unscheduled phone visits may be used, as necessary, to ensure accurate collection of AEs of interest. AEs that are related to study procedures should be recorded in the AE log within the EDC independent of the patient's study drug status or duration since the patient's last dose of study drug.	Clarification on the duration of AE reporting. Extended AE reporting period from 30 days following the last dose to 12 weeks following the last dose of drug, due to the collection of endpoint data through that period.

[redacted]	[redacted]	[redacted]
9.10.34. Tanner Staging	Gender appropriate Tanner staging will be performed on all patients who enroll in the study as adolescents. Tanner staging should be performed at Day 1, Week 52 (B), and Week 108 (B), as outlined in Table 4, to monitor and assess sexual maturity. All assessments must be performed even if a patient reaches 18 years of age while participating in the study. Tanner staging may be performed only by a physician (specifically, the principal investigator or sub-investigator). For further guidance and to access the Tanner Staging see the Study Reference Manual.	A Tanner Staging assessment was added to the protocol, this section was added to outline how and when this assessment will be performed.
9.11. Dose Management	DOSE ESCALATION Both adult and adolescent patients randomized to placebo will remain on placebo throughout the study, undergoing sham titration. Both adult and adolescent patients receiving study drug 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 escalation may need to proceed more slowly if the patient experiences early elevations in ALT/AST over ULN, e.g. at Week 2 (see Section 9.1.2) or if the patient misses visits (see Section during the Dose Escalation Period. 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 1, 2, 4, or 6 with the Medical Monitor. In cases where dose escalation is delayed or not achieved, the investigator should consider dose escalation to goal dose at any time throughout the dosing period.	Relocated and consolidated all dose management text to Section 9.11 (Dose Management).
9.11. Dose Management	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 the dose and must be documented. After dose de-escalation, patients must return for an unscheduled office visit within 4 weeks (± 3 days) to perform the assessments detailed in Section 9.7. If 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 re-escalation and an unscheduled office visit 2 weeks (± 3 days) after dose re-escalation to perform assessments detailed in Section 9.7.	Relocated and consolidated all dose management text to Section 9.11 (Dose Management).

9.11. Dose Management	INTERRUPTION OF STUDY DRUG In addition to dose de-escalation and re-escalation, the study drug administration can be interrupted, if clinically indicated. The term interruption generally refers to a temporary halt of study drug administration. All efforts should be made to resume study drug at any point during the treatment period following interruption, upon consultation with the Medical Monitor. If there are any questions regarding study drug interruption, please consult the Medical Monitor.	Relocated and consolidated all dose management text to Section 9.11 (Dose Management).
9.11. Dose Management	RESUMING STUDY DRUG Any patient who interrupts study drug for 14 consecutive days or more must have approval from the Medical Monitor prior to resuming study drug. When a patient resumes study drug, after an extended interruption (e.g., more than 14 days), the site should discuss the appropriate starting dose and visit frequency with the Medical Monitor. The duration of the interruption and the reason for interruption should be taken into consideration when determining how to safely resume study drug. Following an extended interruption, when the investigator deems it is safe for the patient to return to the site for an in-person visit, the investigator should conduct an evaluation to determine whether the patient is still eligible to receive study drug and to determine the appropriate dose, in consultation with the Medical Monitor. This should include a confirmation that the patient's circumstances have not changed in a manner that would prohibit administration of the study drug (e.g., the patient is now taking an excluded medication). Once the investigator determines study drug administration is appropriate, dosing may proceed. Patients must have a telephone call 1 week after resuming and an unscheduled office visit 2 weeks (± 3 days) after resuming study drug to perform assessments detailed in Section 9.7. For additional guidance on resuming drug following a positive COVID-19 test, see Section 9.11.5.	Relocated and consolidated all dose management text to Section 9.11 (Dose Management).
9.11.3. Post- Week 12 Visits – Missed In-Person Visits	If no in-clinic visit can be completed and remote assessments/laboratory samples cannot be collected within a reasonable time, based on the investigator's discretion, the investigator should consider whether de-escalation may be appropriate.	Language added to defer to investigator's clinical judgement regarding dose de-escalation in the event of a missed visit.
9.11.4. Dose De-Escalation and Interruption for Missed Safety and Laboratory Assessments	~~If no in-clinic visit is completed and remote assessments/laboratory samples cannot be collected within the per protocol allowed time window for that visit, the study drug dose must be de-escalated to the previous dose within 6 days of the protocol visit window. For patients on 5 mg, the lowest dose, the dose may be maintained, and no de-escalation is required. All efforts should then be made to collect laboratory samples. However, if laboratory samples cannot be collected within 14 days from the date of dose de-escalation (for visits through Week 12) and within 28 days (for visits beyond Week 12), 5 mg study drug must be continued until safety lab values can be evaluated and it is deemed appropriate to dose-escalate. Section 9.11.5 describes the procedure for resuming and dose-escalating study drug following drug interruption.~~	Language was moved from section 9.11.4 to section 9.11

<table>
<tr><td></td><td>From Protocol Version 7.0 forward, this text was removed, and language was placed within Section 9.11.</td><td></td></tr>
<tr><td>9.11.5. Resuming ~~or Dose Escalating~~ Study Drug After COVID-19 Interruption or ~~Changes~~</td><td>Patients who interrupt study drug due to a positive COVID-19 test may resume study drug without an in-clinic visit, at the investigator's discretion, ~~of~~ if COVID-19 symptoms are mild, and if the duration of interruption did not exceed 14 days.

~~When the investigator deems it is safe for the patient to return to the site for an in-person visit, the investigator should conduct an evaluation to determine whether the patient is still eligible to receive study drug and to determine the appropriate dose. This should include a confirmation that the reason for interruption was not a per protocol specified reason and that the patient's circumstances have not changed in a manner that would prohibit administration of the investigational~~

Study drug may be resumed when the patient no longer presents an active infection (defined as resolution of symptoms or a negative SARS-CoV-2 test), as assessed by the Investigator and/or the patient's physician(s). If COVID-19 symptoms persist (e.g., loss of taste or smell), the patient should be encouraged to repeat SARS-CoV-2 testing in order to minimize the duration of study drug interruption.

For more information related to study drug management and COVID-19 see Appendix 1, Section 4.5.

~~Once the investigator determines study drug administration is appropriate, dosing may proceed as recommended in the table below.~~

<table><tr><th>~~Study Drug Status~~</th><th>~~Dosing Recommendation~~</th></tr><tr><td>~~Study drug temporarily discontinued for any reason (e.g., COVID-19, delays in obtaining safety lab, AEs)~~</td><td>~~Resume study drug at last administered dose~~</td></tr><tr><td>~~Study drug dose not escalated as required per COVID-19 mitigation plan~~</td><td>~~Continue last administered dose; consider escalating dose, if appropriate~~</td></tr><tr><td>~~Study drug de-escalated for any reason (e.g., due to delays in obtaining safety labs, AEs)~~</td><td>~~Continue last administered dose; consider escalating dose, if appropriate~~</td></tr></table>
~~If the patient is not at the target dose, dose escalation to a higher dose is permitted. Patients who dose escalate must have a telephone call 1 week after dose escalation and an office visit (or unscheduled visit, if necessary) 2 weeks (± 3 days) after dose escalation to collect clinical chemistry, BNP, and NT-proBNP.~~</td><td>Clarified that drug may be resumed without an in-clinic visit, if the interruption is not > 14 days in duration.

Relocated instruction on resuming study drug to main Section 9.11 (Dose Management).

Relocated text from COVID Appendix to this section.

Relocated and consolidated dosing management instructions, and removed redundant text within the protocol.</td></tr>
</table>

	~~Unscheduled visits due to dose escalation should also include assessments detailed in Section 9.7 of the protocol. Once the target dose has been reached and 2-week follow-up completed, the Schedule of Assessments may be resumed.~~	
11.2.1.1. Adverse Event	All AEs that are observed or reported by the patient during the study (from administration of the first dose until ~~30 days following administration of~~ the ~~last dose of~~ Week 112 (B) study ~~drug)~~ visit as indicated in ~~Table 4~~Table 4) must be reported, regardless of their relationship to study drug or their clinical significance. For patients who discontinue study drug early (prior to Week 100) and continue to be followed in the study, all AEs should be recorded for 12 weeks following the patient's last dose of study drug. Beyond 12 weeks after the patient's last dose, only those AEs that are relevant to the clinical condition including kidney disease, may have an impact on kidney function, or may impact the interpretation of safety or efficacy data must be reported. AEs that are related to study procedures should be reported independent of the patient's study drug status or duration since the patient's last dose of study drug. SAEs, if considered related to study drug, can be reported at any time during the study duration. ~~In addition, as noted in Section 11.2.1.2, death, initiation of dialysis, or transplant should be reported through Week 112, on the appropriate eCRF.~~	Clarification on the duration of AE reporting. Extended AE reporting period from 30 days following the last dose to 12 weeks following the last dose of drug, due to the collection of endpoint data through that period.
11.2.1.2. Serious Adverse Event	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~~ Week 112 (B) study visit indicated in Table 4, as appropriate). Certain pregnancy outcomes will require submission as an SAE (see Section 9.8). The investigator is responsible for reporting to Reata or designee all AEs and SAEs that are observed or reported by the patient during the study (from the time of administration of the first dose of study drug until the ~~final~~ Week 112 (B) study visit indicated in Table ~~4, as appropriate),~~), including events resulting from protocol-associated procedures as defined in relevant legislation, and regardless of their relationship to study drug or their clinical significance. For patients who discontinue study drug early, SAEs should be reported through ~~30 days~~12 weeks following the date of last dose of study drug. SAEs, if considered related to study drug, should be reported at any time during the study. ~~In addition, death, initiation of dialysis, or transplant should be reported through Week 112, on the appropriate eCRF. (see Section 11.7).~~ For information on ESKD related SAEs see section 9.1.9.	Clarification on the duration of AE reporting. Extended AE reporting period from 30 days following the last dose to 12 weeks following the last dose of drug, due to the collection of endpoint data through that period.
11.6. Reporting Adverse Events	All conditions present prior to the administration of the first dose of study drug (Day 1) should be documented as medical history. After the first dose, documentation of AEs shall continue until the ~~last~~ Week 112 (B) study ~~follow-up~~ visit, as indicated in Table 4, regardless of ~~the~~ their relationship ~~of the AE~~ to study drug or their clinical significance. For patients who discontinue study drug early (prior to Week 100) and continue to be followed in the study, all AEs should be recorded for 12 weeks following the patient's last dose of study drug. Beyond 12 weeks after the patient's last dose, only those AEs that are relevant to the clinical condition including kidney disease, may have an impact on kidney function, or may impact the interpretation of safety or efficacy data must be reported.	Clarification on the duration of AE reporting. Extended AE reporting period from 30 days following the last dose to 12 weeks following the last dose of drug, due to the collection of endpoint data through that period.

	AEs that are related to study procedures should be reported independent of the patient's study drug status or duration since the patient's last dose of study drug.	
11.6. Reporting Adverse Events	For guidance on how to handle AEs that change in severity (e.g., worsening or improving), see the eCRF Completion Guidelines. All drug-related (possibly, probably, or definitely related, see Section 11.4) AEs and clinically significant abnormal laboratory test results reported or observed during the study must be followed to resolution (either return to baseline, within normal limits, or stabilization). All ~~other~~ non-drug related AEs or clinically significant abnormal laboratory test results will be followed through the ~~30 days after~~ Week 112 (B) study visit or for 12 weeks following the last dose ~~of~~ for patients who discontinue study drug early.	Extended AE reporting period from 30 days following the last dose to 12 weeks following the last dose of drug, due to the collection of endpoint data through that period..
18. References	Marshall WA and Tanner JM. Variations in Pattern of Pubertal Changes in Girls. 1969;44:291-303.	Reference added
Appendix 1. COVID-19 Mitigations 2. COVID-19 Infected Patients and Study Drug Use	Patients who interrupt study drug due to a positive COVID-19 test may resume study drug without an in-clinic visit, at the investigator's discretion, if COVID-19 symptoms are mild, and if the duration of interruption did not exceed 14 days. The maximum duration of treatment interruption due to COVID-19 infection must be determined based on the patient's symptoms and the investigator's discretion. Instructions for how to resume study drug (i.e., appropriate dose for restarting and appropriate visit schedule) are contained in Section 9.11. Additional instructions on resuming study drug are provided in Section 9.11.	Added based on health authority feedback seeking definition of the maximum treatment interruption due to COVID-19 infection and time limit in which the patient must meet with the investigator after treatment is resumed.
Appendix 1. COVID-19 Mitigations ~~4. Study Visits~~	~~4. Study Visits~~ ~~For continued patient safety oversight, patients should continue with protocol-specified visits. Where inadvisable for the patient to be seen for an in-person clinic visit or if a patient is unwilling to come to the clinic, alternate visit completion methods should be considered, such as by phone, telemedicine, home health visits and/or local laboratory monitoring of safety labs.~~ ~~Visits conducted over the phone (or via telemedicine, if available), at a minimum should include the following assessments:~~ ~~• Adverse event assessment~~ ~~• Prior and concomitant medication assessment~~ ~~In-home visits at a minimum should include the following assessments:~~ ~~• Safety labs (may also be done by local laboratories)~~	Relocated the "Study Visit" section from Appendix 1 to Appendix 2. Home healthcare can be used for reasons outside of COVID-19, therefore removed from the COVID-19 Appendix.

	~~– Clinical chemistry (including eGFR)~~ ~~– BNP and NT-proBNP~~ ~~– Hematology~~ ~~– Urinalysis and microscopy / Urine collection for ACR~~ ~~– Urine pregnancy test for WOCBP~~ ~~• Vital signs~~ ~~• Weight at home~~ ~~• Adverse event assessment~~ ~~• Prior and concomitant medication assessment~~	
Appendix 2. Use of Home Healthcare	For continued patient safety oversight, patients should continue with protocol-specified visits. Where inadvisable for the patient to be seen for an in-person clinic visit or if a patient is unwilling to come to the clinic, alternate visit completion methods should be considered, such as by phone, telemedicine, home health visits and/or local laboratory monitoring of safety labs. Visits conducted over the phone (or via telemedicine, if available), at a minimum should include the following assessments: • Adverse-event assessment • Prior and concomitant medication assessment In-home visits at a minimum should include the following assessments: • Safety labs (may also be done by local laboratories) – Clinical chemistry (including eGFR) – BNP and NT-proBNP – Hematology – Urinalysis and microscopy / Urine collection for ACR – Urine pregnancy test for WOCBP • Vital signs • Weight at home • Adverse event assessment	Created a new Appendix specific to the use of home healthcare. Home healthcare can be used for reasons outside of COVID-19, therefore removed from the COVID-19 Appendix.

	• Prior and concomitant medication assessment • Height	

AMENDMENT CHANGE SUMMARY DOCUMENT

CLINICAL STUDY PROTOCOL 402-C-1808

Study Title: A Phase 3 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with Autosomal Dominant Polycystic Kidney Disease (FALCON)

Protocol History

Version 6.0 – 04 February 2022
Version 5.1 – 30 March 2021
Version 5.1 United Kingdom – 30 March 2021
Version 5.1 Germany – 30 March 2021
Version 5.0 – 25 February 2021
Version 4.1 Czech Republic – 28 August 2020
Version 4.1 United Kingdom – 25 June 2020
Version 4.1 Germany – 25 June 2020
Version 4.0 – 25 June 2020
Version 3.1 United Kingdom – 09 January 2020
Version 3.1 Germany – 19 December 2019
Version 3.1 Czech Republic – 18 November 2019
Version 3.0 – 16 July 2019
Version 2.0 – 04 March 2019
Version 1.0 – 12 December 2018

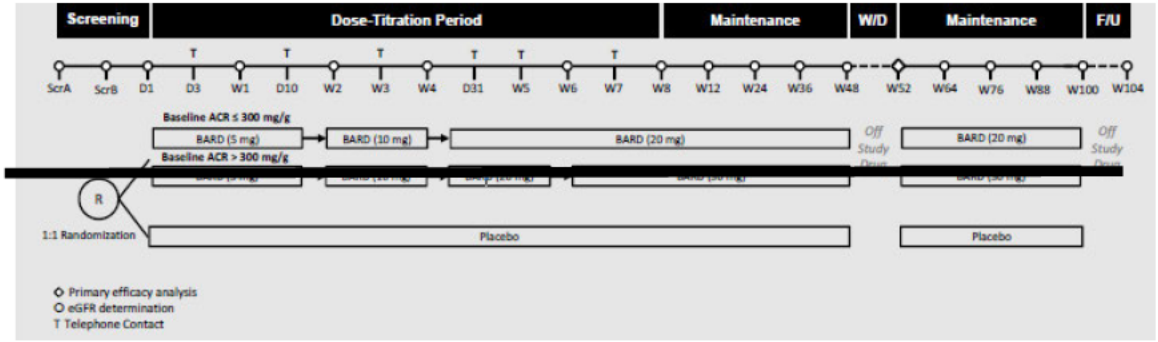
CONFIDENTIALITY STATEMENT

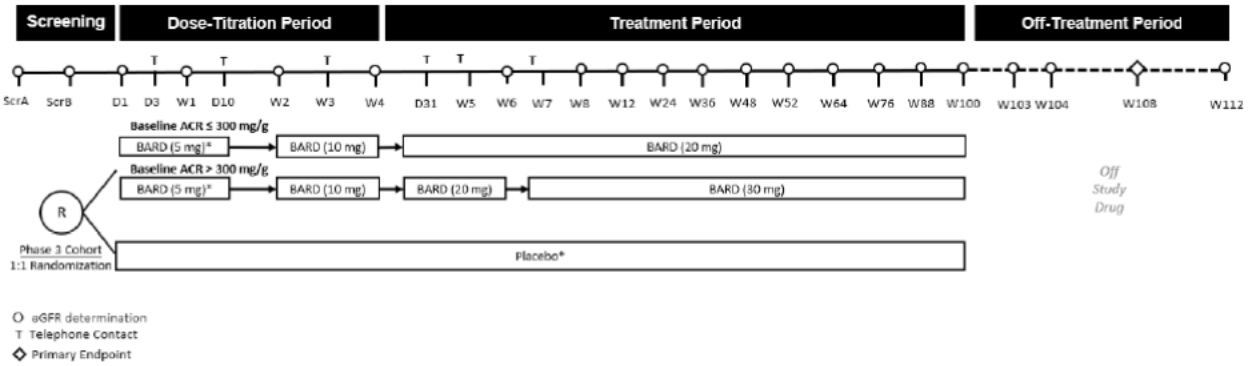
SUMMARY OF CHANGES

The following document outlines the changes made to Version 5 to produce the text of Version 6. Additionally, the following points are provided:

- New text added is underscored; deleted text is designated by ~~strikethrough~~.
- The changes made in the body of the protocol are reflected in the synopsis; the corresponding changes made in the synopsis are not described.
- Grammatical corrections and minor editorial changes are not described.
- Section numbers refer to the numbers in the new version of the protocol.

Section	Version 6	Rationale
Title Page	RTA 402 402-C-1808 US NCT~~IND~~ NUMBER: ~~140817~~NCT03918447 Version 6~~5~~.0 – ~~25 FEBRUARY 2021~~ 04 FEBRUARY 2022 **Protocol Version History** Version 5.1 – 30 March 2021 Version 5.1 United Kingdom – 30 March 2021 Version 5.1 Germany – 30 March 2021 Version 5.0 – 25 February 2021 Version 4.1 Czech Republic – 28 August 2020 Version 4.1 United Kingdom – 25 June 2020 Version 4.1 Germany – 25 June 2020 Version 4.0 – 25 June 2020 Version 3.1 United Kingdom – 09 January 2020 Version 3.1 Germany – 19 December 2019 Version 3.1 Czech Republic – 18 November 2019 Version 3.0 – 16 July 2019 Version 2.0 – 04 March 2019 Version 1.0 – 12 December 2018	Updated NCT number and versioning/date
Sponsor Approval and Signature Page	[redacted]	Updated information

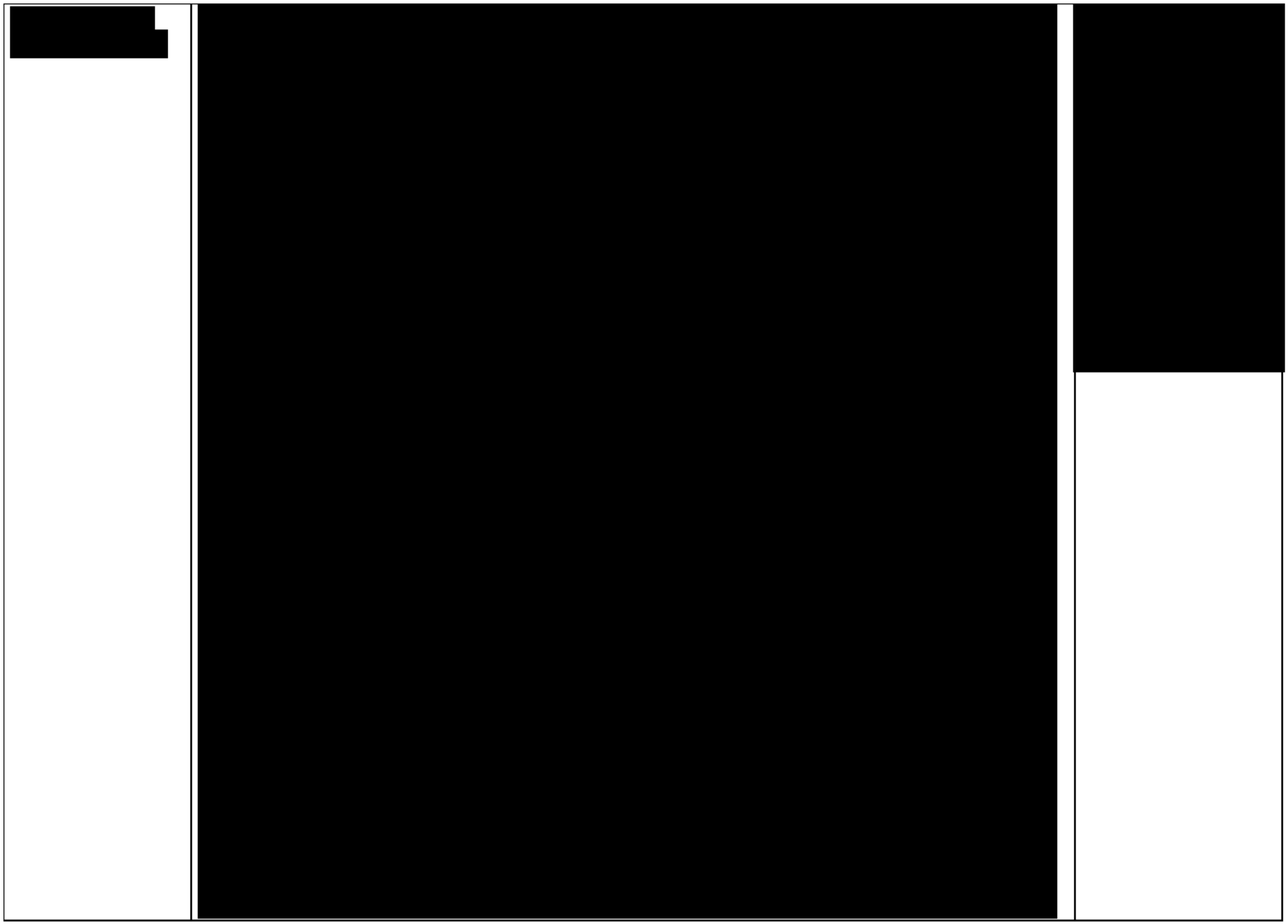
Section	Version 6	Rationale
	[redacted], M.S. [redacted], M.S. [redacted], M.D. [redacted]	
TABLE 1: Emergency Contact Information	[redacted] ~~, M.D.~~ [redacted], M.D. [redacted] [redacted] FALCONmedmon@reatapharma.com	Updated contact information
2. Synopsis, Schema	**Schema for Study of Bardoxolone Methyl in Patients with ADPKD:** 	Schema updated to reflect the removal of the off-treatment (W/D) period between Weeks 48 to 52, the extended off treatment period that follows Week 100, from a 4-week duration to a 12-week duration, and the required visits during the off-treatment period.

Section	Version 6	Rationale
		
4. List of Abbreviations and Definitions	ABPM – Ambulatory Blood Pressure Monitoring CGMP – Current Good Manufacturing Practices ~~IP – Investigational Product~~ PT - Prothrombin Time	Updated abbreviations
5.1.2.2. Transaminase and Gamma-Glutamyl Transpeptidase (GGT) Elevations	These increases were not associated with elevations in bilirubin, and hepatotoxicity has not been observed ~~or other signs of liver toxicity~~.	Updated to reflect a request received from regulatory agency.
6.1.1. Primary Objective	• To assess the off-treatment change from baseline in estimated glomerular filtration rate (eGFR) at Week ~~52~~ 108 ~~or following a 4-week drug treatment withdrawal period in the first year of treatment~~.	Change in primary objective to evaluate efficacy at end of Year 2 (instead of at end of Year 1), based on regulatory agency feedback on adequacy of off-treatment period.
6.1.2 Secondary Objective	~~• Key Secondary Objective~~ ~~To assess the off-treatment change in eGFR at Week 104 or following a 4-week drug treatment withdrawal period, in the second year of treatment.~~ • Secondary Objective	Change in primary objective to evaluate efficacy at end of Year 2 (instead of at

Section	Version 6	Rationale
	~~To assess the change from baseline in eGFR after 48 weeks of treatment~~ • To assess the change from baseline in eGFR ~~after~~ at Week 100. ~~weeks of treatment.~~	end of Year 1), based on regulatory agency feedback, resulted in the removal of the key secondary objective, and adjustment of the remaining secondary objective.
[redacted]	[redacted]	[redacted]

Section	Version 6	Rationale
	[redacted]	
6.2.1. Primary Efficacy Endpoint	• Off-treatment change from baseline in eGFR at Week ~~52~~ 108 ~~(or following a 4-week drug treatment withdrawal period in the first second year of treatment).~~	Change in primary objective to evaluate efficacy at end of Year 2 (instead of at end of Year 1), based on regulatory agency

Section	Version 6	Rationale
		feedback on adequacy of off-treatment period.
6.2.2 Secondary Efficacy Endpoints	• ~~Key Secondary Efficacy Endpoint~~ – ~~Off treatment change from baseline in eGFR in Week 104 (or following a 4 week drug treatment withdrawal period in the second year of treatment.~~ • Secondary Efficacy Endpoints – ~~Change from baseline in eGFR at Week 48.~~ – Change from baseline in eGFR at Week 100.	Change in primary endpoints from Year 1 to Year 2 due to removal of interim database lock at year 1, resulted in removal of the key secondary efficacy endpoint and adjustment of the remaining secondary efficacy endpoint.



Section	Version 6	Rationale
	[redacted]	
7.1. Overall Study Design	Approximately ~~550~~ 850 patients will be enrolled. 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, 12, 24, 36, 48, 52, 64, 76, 88, and 100, ~~and 104,~~ and by telephone contact on Days 3, 10, 21, 31, 38, and 45. Patients ~~will not receive study drug during a 4-week withdrawal period between Weeks 48 and 52. They will re-start treatment at Week 52 at the same dose they were receiving at Week 48 and~~ will continue study drug treatment through Week 100. Patients will also be scheduled to be assessed at an in-person follow-up visit at Weeks 103, 104, 108, and 112 after the end of treatment, respectively. ~~four weeks after the end of treatment.~~ ~~The primary efficacy endpoint~~ Efficacy endpoints will be analyzed after all enrolled patients have completed the study and the database has been locked. ~~their Week 52 visit (or have terminated from the trial). The key secondary efficacy endpoint will be analyzed after all enrolled patients have completed their Week 104 visit (or have terminated from the trial).~~ All enrolled patients are expected to remain on	Update in primary endpoint that impacts the sample size since the W108 value will be used for endpoint analysis, regardless of how long a patient has been off treatment. A dilution in the difference between treatment groups at Week 108 is expected due to contribution of early treatment discontinuation patients

Section	Version 6	Rationale
	their blinded treatment assignment through Week 100, and to complete all scheduled assessments through Week ~~104~~ 112. ~~Results at Week 52 will not impact the study design for the 2nd year of the trial. Details of the Week 52 analysis, including firewalls to ensure integrity of the 2nd year of the trial, will be specified in the SAP.~~	who received a shortened treatment duration and have a longer untreated period associated with natural disease progression. Therefore, the expected treatment effect is reduced from 3.1 to 2.3 mL/min/1.73m^2. Additionally, the assumed variability was increased based on observed variability at Week 104 in the completed 1603 Phase 3 study and a longer off-treatment period for the primary endpoint. The sample size was increased from 550 to 850 to account for the change in expected treatment effect and increased variability. Assessment schedule updated to omit the off-treatment period between Week 48 and Week 52 based on updated endpoints.
7.2 Number of Patients	Approximately ~~550~~ 850 patients will be enrolled.	Increased sample size to reflect updated primary endpoint analysis. See

Section	Version 6	Rationale
		explanation above from 7.1 Overall Study Design.
7.3 Treatment Assignment and Dosing Rationale	Patients will be randomized 1:1 to either bardoxolone methyl or placebo. Randomization will be performed using an interactive web response system (IWRS). Patients randomized to placebo ~~in the Phase 3 cohort~~ will remain on placebo throughout the study but will follow sham titration to maintain the blind. The use of a placebo comparator is justified because the known safety profile of tolvaptan, which is approved for the treatment of ADPKD in adults with evidence of rapidly progressing disease, together with the known pharmacologic effects of bardoxolone methyl, could complicate safety monitoring and medical management of patients in a double-blind trial. A placebo-controlled trial with bardoxolone methyl provides the best opportunity to determine the benefit-risk profile for bardoxolone methyl in ADPKD patients. The same dose titration regimen was ~~successfully~~ used in a Phase 2 trial in adult ADPKD patients (study 402-C-1702).	Updated to better characterize the safety profile of the investigational product.
7.3.1 Adolescent Dosing Rationale	Adolescents (12 ≤ age < 18) will receive the same dosing regimen as adults. The maximum bardoxolone methyl dose will be determined by baseline proteinuria status. Similar to the adult population, a 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. Although no adolescent (12 ≤ age < 18) patients with CKD due to ADPKD have been exposed to bardoxolone methyl, in Study 402-C-1603 (CARDINAL) phase 2/3 studies and an open-label extended access study in Alport syndrome (Study 402-C-1803, EAGLE), a total of 21 adolescent patients received bardoxolone methyl at a maximum dose of 20 mg for patients with baseline ACR ≤ 300 mg/g and a maximum dose of 30 mg for patients with baseline ACR > 300 mg/g. In CARDINAL phase 2/3 studies, the dose titration for adolescent patients was similar to adults, differing only during the first week, where adolescents administered study drug (at the 5 mg dose) every other day, while adults (also at the 5 mg dose) administered study drug daily. An overall safety/tolerability evaluation of adolescent patients from CARDINAL phase 2 (open-label- n=2) and Phase 3 (double-blind placebo-controlled – n=11) showed the dosing regimen was well tolerated and the adverse event profile in adolescent patients was similar to the adverse events profile observed in the adult patients.	Updated to provide dose rationale for adolescents (12 ≤ age < 18).

Section	Version 6	Rationale
	Additionally, a population pharmacokinetic (popPK) analysis was conducted for bardoxolone methyl using rich and sparse PK data from 8 clinical studies in healthy subjects and patients with Alport syndrome, PAH, T2DM CKD, ADPKD, and other rare CKDs (Study REAT-BARD-PMX-1532). The effects of intrinsic factors on bardoxolone methyl PK were evaluated in the popPK analysis and showed that no dose adjustments based on sex, age, body weight, race, or renal function are needed. To further support dosing recommendations based on age, simulations using the popPK model were performed to assess the potential effects of age on bardoxolone methyl steady-state exposures. Simulations were conducted following 20 mg QD and used individual posthoc PK parameter estimates for all patients and subjects in the popPK analysis dataset. Model predictions demonstrate a lack of a clinically meaningful difference in exposures between patients and subjects <18 years of age and patients and subjects ≥18 years of age (ratio of median exposures: 0.93 to 1.11). In addition, the systemic clearance of bardoxolone methyl was not affected by disease state in the popPK analysis. Therefore, there are no differences in systemic exposure (AUC) expected between patients with ADPKD and patients with Alport syndrome. The popPK model predicted mean steady-state AUC for patients receiving 30 mg QD (n=16) in Study 402-C-1702 (rare CKDs, including ADPKD) is 222 ng*hr/ml (SD = 134 ng*hr/ml), and is similar to the popPK model predicted mean steady-state AUCs of 263 ng*hr/ml (SD = 135 ng*hr/ml) and 223 ng*hr/ml (SD = 155 ng*hr/ml) in Alport syndrome patients receiving 30 mg QD in the phase 2 (n=9) and phase 3 (n-24) portions of Study 402-C-1603), respectively. In summary, there were no differences in adverse event profiles in adolescent and adult patients who received bardoxolone in CARDINAL phase 2/3 studies, and a popPK analysis suggested there are no expected differences in systemic exposure (AUC) between ADPKD and Alport syndrome patients and no age dependent requirements for dose adjustments. Therefore, the same dosing regimen is proposed both for adolescent and adult ADPKD patients.	
7.3.2. Dose Escalation	In cases where dose escalation is delayed or not achieved ~~prior to Week 48,~~ the investigator should consider dose escalation to goal dose ~~after study drug is resumed at Week 52~~ at any time throughout the dosing period.	To assess the long-term efficacy and safety of the goal dose.
7.3.3. 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 the dose and must be documented. After dose de-escalation, patients must 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.	Clarification of required study assessments.

Section	Version 6	Rationale
	~~Once~~ If 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 re-escalation and an unscheduled office visit 2 weeks (± 3 days) after dose re-escalation to perform assessments detailed in Section ~~collect clinical chemistry, BNP, and NT-proBNP. Unscheduled visits due to dose escalation should also include~~ 9.7.	
7.3.4. Dose Interruption and Re-Challenge	In addition to dose de-escalation and re-escalation, the study drug administration can be interrupted, if clinically indicated. ~~The term interruption generally refers to a *temporary* halt of study drug administration. All efforts should be made to reinitiate drug after any duration following discontinuation. Is a patient discontinues study drug but continued to be followed in re-challenge the study drug re-challenge should be considered at any point including Year 2 of during the study. All patients treatment period following interruption, upon consultation with the Medical Monitor. If there are any questions regarding study drug interruption, please consult the Medical Monitor.~~ When a patient resumes or re-challenges study drug ~~discontinuation~~, after an extended interruption (e.g., more than several weeks), the site should discuss the appropriate starting dose and visit frequency with the Medical Monitor. The duration of the interruption and the reason for interruption should be ~~discussed with the medical monitor~~ taken into consideration when determining how to safely resume or re-challenge study drug. For detailed instructions on dose management, refer to Section 9.11.	Clarification on the process of re-challenging the investigational product after dose interruption.
Table 4: Schedule of Assessments	A header row was added to denote the Screening Period, including Screen A and Screen B, the treatment period, including Day 1 through Week 100, and the Off-Treatment Period including Weeks 103 through 112B.	Updated the Schedule of Assessments to reflect change in the study design. Header row designates Screening Period, Treatment Period, and Off-Treatment Period for clarity.
	Updated the visit headers to: Screen A Up to Day -90	Added new visit timepoints, clarified

Section	Version 6	Rationale
	Screen B Up to Day -30 ~~Wk 52 (A) Day 363±3 Days~~ Wk 100 or End of Treatment Day 700 -5 Days (+0 Days) ~~±3~~ Off-Treatment: Patients who continue study drug through Wk 100 (visits based on date of last dose) Follow-Up: Patients who discontinue study drug early (visits based on Day 1 date) Wk 103 Day 21 – 25 after last dose Day 721 - 725 Wk 104 (A) Day 28 – 35 Days from Last Dose Day 728 – 735 ~~or Follow up A Day 727±3~~ Wk 104 (B) Day 29 – 36 Days from Last Dose ~~or Follow up B Day 728±3~~ Wk 108 (A) 56 – 63 Days from last dose Day 756 – 763 Wk 108 (B) 57 – 64 Days from last dose Day 756 – 763 Wk 112 (A) 84 – 91 Days from last dose Day 784 – 791 Wk 112 (B) 85 – 92 Days from last dose Day 785 – 792	windows, and provided guidance on calculation of off-treatment visits for patients who discontinue drug early versus those who remain on study drug until Week 100.
	Wk 52 (A) Day 363±3 and Wk 52 (B) Day 364±3 were combined into Wk 52 ±3 Days	Removed the second visit at the Week 52 timepoint, given this is no longer the primary endpoint.
	Added PK assessments to Week 100 Added the following visits: Wks 103, 108A, and 112A, which each contain the following assessments: PK (at Wk 103 only), and clinical chemistry (incl. eGFR). Added to Wk 104B: PK samples Added Wk 108B, which includes the following assessments: height, weight in clinic, ECG, vital sign measurement, comprehensive physical exam, pregnancy test for WOCBP, clinical chemistry (incl. eGFR), BNP and NT-proBNP, hematology, coagulation, basic lipid panel, urinalysis and microscopy, urine collection for ACR, [redacted], PK samples, SARS-CoV-2 antibody test, [redacted] Added Wk 112B, which includes the following assessments: blood and urine collection, clinical chemistry, incl eGFR.	Added new visits and assessments to the study design.

Section	Version 6	Rationale
	ABPM added at Screening, Wk 12, Wk 48 and Wk 88 Vital Sign measurements added to Screen B, only if needed for eligibility determination.	
	Abbreviations: ABPM = Ambulatory Blood Pressure Monitoring ~~IP = investigational product~~ IRB/EC = institutional review board/ethics committee IWRS = interactive Web Response System, SARS-Cov-2 = Severe Acute Respiratory Syndrome Coronavirus 2	Updated for clarity. Added and removed abbreviations.
	[a] Total Screening period should not exceed 90 days ~~3 months~~. [e] All patients' height will be recorded in centimeters. Adult patients (18 ≤ age ≤ 70 years at Screen A visit) will be measured at Screen A only. Adolescent patients (12 ≤ age < 18 years at Screen A visit) will be measured at all specified timepoints. [f] An echocardiogram performed ~~at the Screen A visit~~ during screening or within 6 months prior to Day 1 may be used to determine eligibility. ~~[f] Investigator should evaluate if a targeted physical exam is needed, based on any symptomology is reported to the study team~~ [g] Screen B vital sign measurements are needed only if re-assessing blood pressure for eligibility. [j] Kidney ultrasound (historical or one obtained ~~at Screen A~~ during screening) may be used to diagnose ADPKD for patients without a prior ADPKD diagnosis. ~~[k] 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 in the clinic on PK sample collection visits after the 0 hour PK blook sample is collected. Patient will have blood samples for PK analysis prior to (0 hour) and after (2 and 4 hours) dose administration. If PK sampling is unable to be performed during the Week 12 visit, samples may be collected at Week 24, 36, or 48.~~	Clarification within the footnotes.

Section	Version 6	Rationale
	[l] Patients must refrain from taking study drug prior to coming to the clinic for PK draws at Week 12 and Week 100. [m] Ambulatory Blood Pressure Monitoring (ABPM) is an optional sub-study for adult patients (18 ≤ age ≤ 70 years at Screen A) who consent to the procedure. See Section 9.10.33 for details and timing on ABPM. ABPM will not be performed on adolescent patients (12 ≤ age < 18 years at Screen A). [n] For patients who consent to the optional ABPM sub-study, the initial (baseline) 24-hour monitoring assessment must be done during the screening period prior to Day 1. See Section 9.10.33. [o] For patients who consent to the optional ABPM sub-study, the final 24-hour monitoring assessment occurs after Week 88 and prior to Week 100 (last dose). For patients who discontinue study drug prior to Week 100, patients who consented to ABPM should have the assessment at End of Treatment if no ABPM was conducted in the four weeks prior to the date of last dose. [p] See sections 8.3.3 and 8.5.1 for details on the Off-Treatment Period. ~~[l] Both Week 52 visits must be completed 28 to 36 days after last dose in year 1, and before re-dispensing study drug.~~ ~~[m] Patients who terminate from the study drug prior to the Week 100 study visit should be brought back to the clinic as soon as possible for early termination assessments (i.e. end of treatment visit) as well as follow up visits within 28 to 36 days after the last dose.~~ ~~n Both Week 104 visits must be completed 28 to 36 days after last dose in year 2.~~	

Section	Version 6	Rationale
8.1. Patient Inclusion Criteria	1. Male and female patients 12 ~~18~~ ≤ age ≤ 70 upon study consent;	Changing the age of inclusion to study adolescents 12 and above based on feedback from EMA CHMP PDCO.
	2. Diagnosis of ADPKD a. For adult (18 ≤ age ≤ 70 years) diagnosis of ADPKD by modified Pei-Ravine criteria: 1) at least 3 cysts per kidney by sonography or at least 5 cysts by CT or MRI with family history of ADPKD or 2) at least 10 cysts per kidney by any radiologic method and exclusion of other cystic kidney diseases if without family history; b. For adolescent (12 ≤ age < 18 years) diagnosis of ADPKD as defined: 1) by the presence of family history and/or genetic diagnosis and the presence of at least 1 cyst of 0.5 cm on ultrasound or MRI, 2) Patients without a family history or genetic diagnosis must have at least 10 bilateral renal cysts in total, and exclusion of other kidney diseases;	Changes made to inclusion criteria, for adolescent subjects based on Ravine et al established criteria.
	~~3. Screening~~ eGFR ~~(the two values collected at Screen A and B)~~ must: a. Have a percent difference ≤ 25% at screening (the values at Screen A and Screen B) and; b. Have an average (the values at Screen A and Screen B) ≥ 30 to ≤ 90 mL/min/1.73 m^2 for patients 12 ~~18~~ to 55 or ≥ 30 to ≤ 44 mL/min/1.73 m^2 for patients 56 to 70 years, and; c. Support ADPKD disease progression (i.e. average yearly eGFR decline of ≥ 2.0 mL/min/1.73 m^2 for 2 consecutive years) for patients with either screening eGFR ≥ 60 to ≤ 90 mL/min/1.73 m^2 or age 56 to 70 year (see Section 9.10.2). ~~According to the medical monitor, support ADPKD disease progression (i.e., eGFR decline of ≥ 2.0 mL/min/1.73 m2 per year) for patients with either screening eGFR ≥ 60 to ≤ 90 mL/min/1.73 m2 or age 56 to 70 years.~~	Updated to remove Medical Monitor approval and to simplify the language.
	5. Systolic blood pressure ≤ 140 mmHg and diastolic blood pressure ≤ 90 mmHg at Screen A or Screen B visit after a period of rest. Patients receiving an angiotensin-converting enzyme (ACE)* inhibitor and/or an angiotensin II receptor blocker (ARB)* must be on a stable dose for at least 6 weeks prior to the Screen A visit; *see Section 9.1.7	To allow sites a second timepoint to assess blood pressure for eligibility determination, optional BP reading was added

Section	Version 6	Rationale
	9. Evidence of a personally signed and dated informed consent/assent document indicating that the patient has been informed of all pertinent aspects of the study prior to initiation of any protocol-mandated procedures.	at Screen B. Updated to include adolescent assent.
8.2 Patient Exclusion Criteria	2. ~~Concomitant~~ Use of tolvaptan ~~is excluded. Patients previously treated with tolvaptan must have discontinued drug for at least~~ within 3 months prior to Screen A ~~visit~~. Initiation of concomitant tolvaptan use during the study is not permitted;	Updated for clarity.
	22. Coronavirus disease 2019 (COVID-19) ~~diagnosis within 6 months prior to Randomization, with accompanying symptoms~~ pneumonia, related acute kidney injury, or ~~even required COVID-19~~ related hospitalization within 6 months prior to Day 1.	Updated criteria for Coronavirus.

8.3. Screening, Treatment, and Off-treatment Periods	**8.3 Screening, Treatment, and Off-Treatment Periods** ~~The screening period must not exceed 3 months. The Screen B visit should be no more should be than 30 days prior to Day 1.~~ **8.3.1. Screening Period** The screening period begins with the signing of the informed consent/assent at the Screen A visit and ends at the start of the Day 1 visit. The duration of the screening period must not exceed 90 days ~~3 months~~. The Screen A procedures may be completed across multiple days. Efforts should be made to ensure the Screen B visit ~~should be~~ is no more than 30 days prior to Day 1. Sites must not initiate screening of an adolescent who will become an adult prior to Day 1. If, at the time of randomization, a patient is an adult, eligibility must be assessed based on the adult eligibility parameters (ADPKD diagnosis and eGFR calculation). Where calculation of the screening eGFR average results in a decimal, basic rounding principles apply. For example, an average eGFR of 29.5 mL/min/1.73 m^2 would round up to 30 mL/min/1.73 m^2. Eligibility should be confirmed prior to randomization of any patient in the IWRS. All screening procedures should be completed per the schedule of assessments in Table 4. **8.3.2 Treatment Period** The Treatment Period refers to the time from administration of the first dose (Day 1 visit) through administration of the last dose (Week 100 visit). Administration of the first dose of study drug should occur in-clinic, at the Day 1 visit, after confirmation of eligibility and randomization. Administration of the last dose of study drug should occur in-clinic, at the Week 100 visit, following the collection of all lab and PK assessments. During the treatment period, sites should ensure proper documentation of any intentional interruptions in dosing, including the reason for and duration of the interruption. Information regarding interruptions should be entered into the clinical database. A patient who discontinues study drug early has a shortened treatment period. Regardless of when a patient's treatment period ends, it is imperative that an off-treatment period follows study drug discontinuation. See Section 8.3.3 for required assessments in the Off-Treatment Period.	Added general guidance regarding each period of the study (Screening, Treatment, Off-Treatment). Screening Period: Added language to avoid adolescent patients screening for the study, if the patient will become and adult prior to Day 1. Added guidance on calculation of average eGFR, and how decimals should be handled, for eligibility determination. Treatment Period: Added general guidance.

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	If a patient resumes study drug, the patient should resume the normal study schedule and follow instructions in Section 7.3.3 regarding dose interruption and re-challenge. All assessments during the Treatment Period should occur per the Schedule of Assessments, in Table 4. **8.3.3 Off-Treatment Period** The purpose of the Off-Treatment Period is to continue assessing patients for 12 weeks after patients have completed 100 weeks of study drug administration (or after the last dose of study drug if a patient discontinues study drug early). The Off-Treatment Period visits are of critical significance to this study. Every effort should be made to obtain off-treatment assessments following any discontinuation of study drug, whether at the planned Week 100 timepoint or at an earlier timepoint during the study. For patients who remain on study drug through Week 100, the planned Off-Treatment Period begins the day after the Week 100 visit and continues through Week 112. Patients must complete 7 visits during the Off-Treatment Period, as listed in Table 4, and as described below: • Week 103 visit (21 – 25 days from date of last dose) • Week 104 A & B visits (28 – 36 days from date of last dose) at least one day apart • Week 108 A & B visits (56 – 64 days from date of last dose) at least one day apart • Week 112 A & B visits (84 – 92 days from date of last dose) at least one day apart To the extent possible, sites should try to avoid bringing patients in very late in the window for a particular visit, and then very early in the window for the next timepoint. For example, a patient who completes Week 104 A & B visits 35 and 36 days after last dose, then completes Week 108 A & B visits 56 and 57 days after last dose, would have Week 104 and Week 108 visits spaced only 20 days apart, rather than ~4 weeks apart. Sites should attempt to achieve an approximate 4-week interval between Weeks 100, 104, 108, and 112. For patients who discontinue study drug prior to Week 100, the patient should be assessed at the following timepoints, see Table 4 for full list of assessments: • An End of Treatment visit as close as possible to the last dose • One visit 3 weeks after discontinuation (21 – 25 days from date of last dose) • Two visits 4 weeks after discontinuation (28 – 36 days from date of last dose) at least one day apart • Two visits 8 weeks after discontinuation (56 – 64 days from date of last dose) at least one day apart	Off-Treatment Period: Added language to ensure understanding of the purpose of the extended Off-Treatment Period, and to ensure completion of the required visits for patients who remain on study drug, and those who discontinue study drug early.

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	• Two visits 12 weeks after discontinuation (84 – 92 days from date of last dose) at least one day apart For patients who discontinue study drug early, after the above Off-Treatment Period is completed, the patient will continue with all assessments through Week 112, except PKs and ABPM (if applicable). See section 8.5.1 for detail regarding the importance of continued follow-up for patients who discontinue study drug early. AEs should be reported for 30 days following the patient's last dose of study drug.	
8.4.1 Re-Screening	Patients may repeat ~~the~~ Screening ~~procedures~~ once to qualify for the study (re-screening must occur at least 2 weeks after the screen fail). In rare circumstances, a second re-screening may be appropriate; in these cases, the site must consult with the Medical Monitor for approval. ~~If~~ When a patient repeats screening, the patient is ~~approved to re-screen, they are~~ given a new patient number and ~~all~~ re-screening procedures are completed under the new patient number.	Updated for clarity.
8.4.2. Re-Testing	In rare situations, a specific screening test may be repeated if the test value (e.g., BNP) is inconsistent with the patient's medical history and/or is considered by the investigator to be an anomaly. Medical Monitor approval must be obtained prior to re-testing any of the eligibility parameters for a patient.	Updated for patient safety review.
8.5 Patient Discontinuation and Termination	Patients have the right to discontinue study drug or withdraw from study follow-up at any time for any reason, without prejudice to their medical care. Furthermore, the investigator may discontinue a patient from study drug. The term discontinuation generally refers to a *permanent* halt in study drug administration. Consultation with the Medical Monitor should occur prior to study drug discontinuation. The reason for a patient's discontinuation from study drug or study termination will be recorded in the electronic case report form (eCRF). Any patient ~~that~~ who discontinues study drug for 14 consecutive days or more must have approval from the Medical Monitor prior to resuming treatment with study drug.	Addition of definition for clarity.

8.5.1. Study Drug Discontinuation Criteria	Study drug discontinuation refers to a patient's stopping administration of study drug. Reasons for study drug discontinuation may include the following: • Adverse event; • Death; • Lost to follow-up; • Physician decision; • Pregnancy; • Protocol specified criterion met (Section 7.4, Section 9.1.1, Section 9.1.9, Section 9.3.1, Section 9.6.1, and Section 9.8.3); • Withdrawal by ~~subject~~patient; To maximize patient retention and minimize missing data, patients who ~~are permanently discontinued~~ discontinue ~~from~~ study drug ~~should still~~ early are encouraged to remain active in the study and complete all future study visits and assessment, except PKs and ABPM, if applicable. For patients who discontinue treatment prior to Week 100, see Section 8.3.3 for the required off-treatment assessments. After the off-treatment assessments, the patient will continue with ~~study~~ follow-up, completing all study visits and undergoing all scheduled study assessments through Week ~~104~~ 112. For patients who are unwilling to complete all future visit, the Week 108 visit is of ~~laboratory~~ paramount significance. Collecting Week 108 data ~~and vital status (including ESKD status) through Week 104 is important~~ for all randomized patients is essential for trial integrity~~and data may be obtained through in-person clinic visits or through home health visits. AEs and SAEs should be collected for 30 days following the date of last dose.~~ For patient who ~~permanently~~ discontinue study drug and are no longer willing to return for all scheduled study visits, a number of follow-up options are available and must be discussed with the patient thoroughly, including: • Participation in follow-up procedures specified in the protocol by an in-home visit, where feasible; • Reduced in-person visit schedule; • Telephone contact only; • Contact of alternative person(s) who has been designated in source records as being available to discuss the patient's medical condition;	Off-treatment period is extended to 12 weeks, added language to have same off-treatment visits for subjects who discontinue. Added additional language around visit for clarity.

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	• Non-direct follow-up of patient information including obtaining additional information from the patient's medical records (e.g., ESKD or death). These reduced follow-up options should be discussed with any patient considering study termination following ~~permanent~~ discontinuation of study drug. The frequency and schedule of participation in follow-up procedures, whether in-clinic, by telephone, by in-home visit(s) or some other means, should be discussed and agreed to by patient and staff. All efforts to prevent the patient from progressing to a "Lost to Follow-Up" status must be made ~~at the time of permanent study drug discontinuation.~~ Any discussions about reduced follow-up options must be documented in the patient's source file ~~and discussed with the study manager~~. ~~A patient who permanently discontinues treatment anytime prior to Week 100 will have an end of treatment visit as close as possible to the day of last dose. The patient will then complete both Follow-up A and Follow-up B visits within 28 to 36 days after last dose. Safety and clinical chemistry assessments, including a serum creatinine assessment for efficacy, will be performed at the end of treatment and follow-up visits. After the follow-up visits, the patient will continue with all assessments up to and including their scheduled Week 52 and Week 104 visits. AEs and SAEs should be reported for 30 days following the patient's last dose of IP.~~ Patient Sites should strongly consider the use of home health care visits to maximize data collected from patients who become unwilling to return for in-clinic visits.	
8.5.2. Patient Study Termination Criteria	Patients should not be considered lost to follow-up until the scheduled Week ~~104~~ 112 visit date. The term "withdrawal of consent" should be used only when the patient no longer wishes to participate in the trial and no longer authorizes investigators to make efforts to continue to obtain their outcome data. Unless the patient provides ~~their~~ written withdrawal of consent or there is other written documentation by the investigator confirming the patient's verbal intent to completely withdraw from the trial, patients should be followed for all protocol specified evaluations and assessments. The investigator should inquire about the reason for withdrawal of consent, request the patient return all unused investigational product, request the patient return for end-of-treatment and follow-up visits (if applicable), and follow-up with the patient regarding any unresolved AEs. Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent or assent, if applicable. The reasons for a patient's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the patient and the integrity of the trial.	Update visit number based on added Week 112 visit.

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	Only patients who withdraw ~~their~~ permission for all ~~of the~~ follow-up options outlined in Section 8.5.1 are considered to have completely withdrawn their consent to participate in the study	
9.1.1. Management of Fluid Status	Laboratory data and rapid weight gain will also be used to monitor fluid status after randomization. Patients who experience a BNP > 100 pg/mL that represents a doubling (or more) of BNP levels from Day 1 should have an unscheduled telephone contact immediately ~~(see Section 9.10.15 for description of telephone contact).~~to evaluate for any symptoms of fluid overload, and accordingly, request an unscheduled visit to assess signs and symptoms of congestive heart failure, heart failure, acute pulmonary edema, etc. identified through the telephone contact. In addition, patients will be given a Sponsor-provided scale to use at home to collect and record weights daily during the study. In the event the Sponsor-provided scale is temporarily unavailable (e.g. patient is traveling, replacement scale has not arrived to patient, etc.), patients may use any available scale. Use of a scale other than the Sponsor-provided scale should be documented in the patient diary. Patients who experience a weight increase of three pounds (1.4 kilograms) in a day or five pounds (2.3 kilograms) or greater increase within a week must have an unscheduled telephone contact immediately. Whether prompted by BNP elevations ~~or~~, sudden weight gain, ~~if clinically important fluid retention is suspected,~~ or by the presence of clinical signs and symptoms the patient must be instructed to stop taking their study medication immediately and be medically evaluated by the investigator or a local physician within 1 to 2 days. Investigators are encouraged to consider starting or increasing doses of diuretics (thiazides, loop diuretics) early after recognition of edema. This can be done concurrently with temporary ~~drug~~ discontinuation ~~and re-initiation~~ of the study drug. Patients may not restart their study medication until the investigator has completed and documented an assessment of fluid overload.	Updated to include flexibility in at home weight measurements.

9.1.2. Management of Elevated Transaminase Levels (ALT and/or AST)	For only patients who enrolled under Version 2 of the protocol (only performed in the US at the beginning of the study) and are receiving tolvaptan (JYNARQUE), liver biochemistries (ALT, AST, and/or bilirubin levels) should be monitored according to the relevant package insert/REMS program for tolvaptan. For all patients enrolled, nearly all instances of elevated transaminases due to bardoxolone methyl treatment are expected to be asymptomatic. Some patients may experience more rapid increases in ALT/AST values than others during the dose titration period. Investigators may consider extending the time between each dose increase ~~from two weeks to four weeks~~ to manage ALT/AST elevations. ~~Check transaminase levels (as well as TBL, GGT, alkaline phosphatase (ALP), and International Normalized Ratio (INR)) within 48 to 72 hours if the following occurs:~~ • ~~ALT or AST levels > 3X ULN.~~ ~~Repeat testing every 72 to 96 hours until transaminase levels are below 3X the ULN for at least one week. Testing for patients not located near the investigator (such that it is not practical to return to the site at the required intervals) may be performed by a home health nurse using a central lab kit, or at a local lab and sent to the investigator and medical monitor for review.~~ ~~Discontinue study drug administration temporarily and contact the medical monitor to discuss 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 study drug may be restarted with the Sponsor's approval after the following criteria are fulfilled:~~ • ~~Ultrasound of the hepatobiliary tree;~~ • ~~ALT and AST returned to < ULN;~~ • ~~TBL is within normal range;~~ • ~~Other relevant labs (e.g., albumin, INR, PT) are within normal range;~~	Updated to clarify that version 2 of the protocol was only performed in the US. Updated information into a table format for clarity and understanding.

~~No clinical signs or symptoms of liver injury are present.~~ If a patient's transaminases are elevated, follow the instructions outlined in Table 5.

Table 5: Management of Elevated Transaminase Levels (ALT and/or AST)

ALT and/or AST Level(s)	Dose Interruption (yes/no)	Procedure
> 8x ULN > 5x ULN for more than 2 weeks > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia > 3x ULN and (TBL > 2X ULN **or** INR > 1.5)	Yes	➢ Discontinue study drug temporarily ➢ Contact the Medical Monitor The study drug may be restarted with Sponsor approval after all the following criteria are met: • Ultrasound or MRI of the hepatobiliary tree*; • ALT and AST returned to ≤ ULN; • TBL is within normal range; • Other relevant labs (e.g., albumin, INR, PT) are within normal range; • No clinical signs or symptoms of liver injury are present. *Based on imaging results, if additional tests/studies are warranted, this should be discussed with the Medical Monitor.
> 3x ULN	No	➢ Check transaminase levels (as well as TBL, GGT, alkaline phosphatase (ALP), and International Normalized Ratio (INR)) within 48 to 72 hours Continue testing for ALT/AST every 72 to 96 hours until transaminase levels are below 3X the ULN for at least one week

Patients restarting study drug should start at the 5 mg dose level and dose titrate according to Section 7.3.~~2~~3.

Language was modified to align with clinical practices in the study.

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	The hepatobiliary tree must be ~~visualized (e.g., assessed by~~ ultrasound~~.~~ or magnetic resonance imaging [MRI~~]) and assessed if a patient meeting above~~] for patients who meet temporary discontinuation criteria ~~discontinues taking study drug . Additional~~. Based on imaging results, if additional tests/studies ~~may be~~ are warranted ~~depending on~~ , this should be discussed with the ~~clinical presentation.~~ Medical Monitor.	
9.1.9. End Stage Kidney Disease	Two off-treatment serum creatinine assessments should be collected 28 to 36 days after last dose, and prior to initiation of dialysis or receipt of transplant. Upon initiation of dialysis, study drug should be ~~temporary discontinued~~ interrupted. Because laboratory and vital sign assessments can be affected by receiving dialysis, those safety assessments should not be performed concurrently while a patient is receiving dialysis. Patients receiving dialysis should continue to be followed for vital status and SAEs by phone or in-person according to the protocol scheduled visits. Dialysis not lasting at least 12 weeks will be considered acute dialysis, and patients should be considered for re-initiation of study drug with Medical Monitor approval. Such patients should continue to undergo frequent follow-up (i.e., at least once every 4 weeks (± 2 weeks)) while eGFR ≤ 15.0 mL/min/1.73 m^2. Study drug may be re-started following acute dialysis, with Medical Monitor approval. Dialysis lasting at least 12 weeks will be confirmed as maintenance dialysis. Upon confirmation of maintenance dialysis, study drug should be ~~permanently~~ discontinued. Upon receipt of kidney transplant, study drug should be ~~permanently~~ discontinued. Following ~~permanent~~ study drug discontinuation due to confirmation of maintenance dialysis or receipt of kidney transplant, patients should continue to be followed only for vital status and SAEs by phone or in person according to the planned contact schedule in Section 7.5 through their scheduled Week ~~104~~ 112 visit date. See Section 8.5 for description of follow-up options following ~~permanent~~ study drug discontinuation. Initiation of dialysis (acute and/or maintenance) and receipt of kidney transplant due to end stage kidney disease should be considered important medical events, and as such recorded as SAEs.	Updated visit number based on the extended Off-Treatment Period, which continues to Week 112.
9.2 Description of Study Drug	Bardoxolone methyl (RTA 402) drug product information is shown in ~~Table 5~~Table 6. Information about the placebo is shown in Table 7 ~~Table 6.~~ Table ~~5~~ 6: Bardoxolone Methyl Drug Product Information Table ~~6~~ 7: Placebo Information	Updated table number.

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9.3.1.1 Excluded Medications	Patients taking these medications or treatments will be ineligible for enrollment: • Tolvaptan (patients on tolvaptan who have already enrolled under Version 2 of the protocol may remain in the trial); • Somatostatin analogues • Any other investigational drug or device as part of an interventional study within 30 days prior to Day 1; • Chronic (> 2 weeks) immunosuppressive therapy, or need for corticosteroids, including therapies such as glucocorticoids, oncologic preparations, and anti-TNFα agents [e.g., infliximab (Remicade®), adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®)] within 12 weeks prior to randomization. Glucocorticoid intra-articular injections, inhaled products, topical preparations, and nasal preparations are allowed. If a patient takes an excluded medication during the study, the investigator should consult with the Medical Monitor immediately to discuss if there is a need for study drug interruption or discontinuation.	Added to provide guidance on acquiring Medical Monitor input.
9.3.1.2 Prohibited Medications	Concomitant use with strong and moderate CYP3A4 inhibitors is prohibited, switching to alternate allowed medication should be considered. If a strong or moderate CYP3A4 inhibitor is medically necessary, discuss with Medical Monitor. Patients who are using these medications prior to screening should have a washout for at least 5-half-life's or 30 days whichever is longer. Concomitant use with strong and moderate CYP3A4 inducers is prohibited, switching to alternate allowed medication should be considered. If a strong or moderate CYP3A4 inducers is medically necessary, discuss with the Medical Monitor. Patients who are using these medications prior to screening should have a washout for at least 5-half-life's or 30 days whichever is longer. Chronic (> 2 weeks) immunosuppressive therapy, or need for corticosteroids, including therapies such as glucocorticoids, oncologic preparations, and anti-TNFα agents [e.g., infliximab (Remicade®), adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®)] within 12 weeks prior to randomization. Glucocorticoid intra-articular injections, inhaled products, topical preparations, and nasal preparations are allowed. Patients who take ~~excluded~~ prohibited 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.	Updated to clearly prohibit concomitant use of strong and moderate CYP3A4 inducers and inhibitors, due to potential drug-drug-interaction of IP when used along with strong and moderate CYP3A4 inhibitors and inducers.

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	~~Concomitant use with strong and moderate CYP3A4 inhibitors is prohibited. If a strong or moderate CYP3A4 inhibitor is medically necessary, study drug must be temporarily discontinued. Concomitant study drug use with strong and moderate CYP3A4 inhibitors must be avoided, and switching to an alternative agent should be considered. Concomitant use with strong CYP3A4 inducers is prohibited~~.	
9.3.2. Permitted Medications	-Antibiotics (~~for~~ if the antibiotic being prescribed is a moderate ~~and~~ or strong CYP3A4 inhibitors and inducers, see section 9.3.1); The list presented above is meant to serve as a broad guideline and is not exhaustive. Drugs not listed here, but which are seemed medically necessary, may be used provided they do not fall in the excluded medications described in Section 9.3.1. Questions about permitted medications should be directed to the Medical Monitor.	To align with sections 9.3.1.1 and 9.3.1.2.
9.5 Randomization	Randomization should occur on Day 1, as a Day 1 study procedure. Where this is not possible, due to logistical issues at the ~~level~~ site, and randomization occurs prior to Day 1, this will result in a protocol deviation. When randomization occurs prior to Day 1, the site must confirm eligibility prior to randomizing the patient in the IWRS and again prior to dispensation of IP at the Day 1 visit.	Updated for clarity.
9.5.1 Blinding	To prevent potential bias, appropriate measures will be taken to ensure the blind is maintained for the patients and personnel ~~mentioned previously~~.	Updated for clarity.
9.6.1 Patient Unblinding	Patients must ~~permanently~~ discontinue taking study drug if their treatment assignment has been unblinded to the investigator (or designee). Such patients must undergo the same study drug discontinuation procedures as those patients who discontinue taking study drug for other reasons. Following ~~permanent~~ study drug discontinuation due to ~~patient unblinded~~ unblinding, patients should continue with study follow-up through their scheduled Week ~~104~~ 112 visit date for vital status only.	Updated for clarity
9.6.3. Data Monitoring Committee	The DMC will consist of external experts supported by an independent statistical group which will prepare unblinded analyses for the DMC and will have no role in the statistical analysis plan (SAP) after the study has started enrolling patients. A separate statistical group not associated with the DMC will be responsible for producing and finalizing the SAP and executing the final data analysis of the study~~, including the Week 52 analysis for the primary endpoint~~.	Removed due to change in primary endpoint.
	Briefly, the DMC will review the progress of the study and the accumulating unblinded data while the study is ongoing. The DMC will make recommendations to Sponsor representatives following each	Removed due to change in primary

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	meeting. The DMC may recommend ~~that~~ the study continue as is, be modified to protect patient safety, or be terminated for safety. The DMC is not expected to make recommendations for the trial based specifically on the ~~Week 52~~ analysis of the primary endpoint. Investigators, not the DMC, will make intra-patient dose-escalation decisions.	endpoint.
9.7. Unscheduled Visits	Unscheduled visits may be performed at any time for any reason, including those not specifically mentioned in this section, as deemed necessary by the investigator. ~~Are allowed for the following reasons:~~ Unscheduled visits conducted for the following reasons should include collection of AEs, clinical chemistry, BNP/NT-proBNP, hematology, concomitant medications collection, and vitals signs: • Assessment of weight gain per Section 9.1.1; • Management of an AE or SAE; • Performance of additional laboratory test for clinically abnormal laboratory test values or to confirm a possible pregnancy; • Dose re-escalation • Dose de-escalation • eGFR ≤ 15.0 per Section 9.1.9; • ~~Any time the investigator feels that it is clinically appropriate for patient safety.~~ Patient safety evaluation Unscheduled visits conducted for the following reasons do not require additional assessments unless deemed necessary by the investigator: • Study drug dispensation • Placement or return of ABPM monitor; • Any operational need that would require the patient to return to the site between scheduled visits. ~~At a minimum, unscheduled visits include collection of AEs, clinical chemistry, hematology, concomitant medication collections, and vital signs, as well as collection/review of weight and dosing diary. Additional conversations may be necessary with the medical monitor following an unscheduled visit to assess patient safety.~~	Added language to emphasize that unscheduled visits may be used at any time and for any reason. Added language to clarify that not all unscheduled visits require collection of labs, etc.
9.8.1 Women of Childbearing	For patients enrolled in the United Kingdom, women with bilateral tubal ligations are considered as WOCBP and will be required to use other types of birth control measures specified in Section 9.8.2	Included UK-specific language in line with local regulatory

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Potential and Fertile Males	Fertile males are those who have entered puberty or reached physical maturation (after puberty~~)~~ and are not surgically sterile (no history of bilateral orchiectomy or vasectomy at least 6 months earlier with the appropriate post-procedure documentation of surgical success).	guidelines in UK, to ensure safety of patient and partners.
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 of a double barrier method 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)) Double-barrier methods are not allowed for patients at participating sites in Germany; During Screening, while taking study drug and until 30 days after the final dose of study medication is taken, fertile males who have female partners of childbearing potential must practice one of the following methods of birth control: - -Use double barrier contraception method, defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream, diaphragm (always use with spermicidal jelly/cream)). Double-barrier method is not allowed for patients at participating sites in Germany; - -Use of hormonal contraceptives (oral, parenteral, intravaginal or transdermal) for at least ~~90~~ 60 days prior to start of study drug administration;	Updated to include clarity on birth control methods in Germany. Updated the required amount of time to be on hormonal contraceptives to align with the WOCBP section.
9.8.3. Suspected Pregnancy	If a WOCBP 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 WOCBP 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~~ she chooses to consent to be followed), 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.	Clarification added to denote this section applies to patients who are WOCBP and to partners who are of WOCBP.

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9.10.1. Informed Consent and Assent	Written informed consent (see Section 15.3) must be obtained from the patient before any study-related procedures are performed~~, and again if~~. Re-consenting will be required when there is ~~a~~ an update or change in the study procedures, safety information, or any other information that ~~would~~ may affect the patient's willingness to participate. For adolescent patients, informed consent will be obtained from the parent(s) or legal guardian in accordance with regional laws or regulations. In addition, dependent upon the patient's age and IRBs, IEC, and/or local requirements, assent of the patient must also be obtained. Adolescent patients may be asked to personally sign and date either a separately designed, written assent form, or the written informed consent. Patients who chose to participate in the Ambulatory Blood Pressure Monitoring sub-study will need to provide written informed consent prior to performing any assessments associated with ABPM. Patients who chose to participate in blood and urine biobanking collection will need to provide written informed consent prior to performing any assessment associated with the specimen collection.	Clarity on assent, consent, and re-consenting process.
9.10.2. Inclusion/ Exclusion	Inclusion and exclusion criteria must be reviewed as indicated in Table 4. Patients must meet all of the inclusion and none of the exclusion criteria for entry in the study. Investigators should contact the Medical Monitor with any questions regarding eligibility prior to randomizing the patient on Day 1. Inclusion 2b, which references genetic diagnosis, may be satisfied by either PKD1 and/or PKD2 gene mutation. Inclusion 3c must show disease progression using average yearly eGFR decline of $\geq$ 2.0 mL/min/ 1.73 m^2 from the last two consecutive years. If a patient has limited historical eGFR values from the past two years, the investigator must discuss the patient's eligibility with the Medical Monitor. Historical eGFRs used to determine eligibility must be well documented in the patient's source.	Added language to clarify inclusion criteria.
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 includes the collection of historical serum creatinine values for the purpose of calculating historical eGFR values. Where possible, sites should obtain historical lab reports from the patient, and enter into the EDC approximately one historical value per year, for the prior 5 years. Medical history will be recorded as indicated in Table 4.	Added language to clarify inclusion criteria.

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9.10.6 Height	Height should be measured without footwear or prosthetics ~~as indicated~~ using a wall-mounted stadiometer. For adult patients (18 ≤ age ≤ 70 years), height is measured at Screen A. Adolescent patients (12 ≤ age < 18 years), height is measured at the timepoints specified in Table 4. Height should be recorded in centimeters, and where height is measured in inches, the following formula should be used to convert inches to centimeters: Height (in inches) x 2.54 = Height (in centimeters) Any conversions of units should be documented in the source documents.	Assessment of height required to calculate eGFR in adolescent patients.
9.10.7 Weight and Body Mass Index (BMI)	Weight must be measured as indicated in Table 4. BMI will be calculated in the eCRF each time the weight is recorded. The Sponsor will provide 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 study, weights will be recorded daily. Patients will be instructed to stop administering study drug and contact the investigator if their daily weight increases per the criteria outlined in Section 9.1.1. Patients will be provided instructions within the Informed Consent Form and/or Assent Form to help ensure consistent weight collection throughout the study. Weight should be recorded in kilograms, and where weight is measured in pounds, the following formula should be used to convert pounds to kilograms: Weight (in pounds) ÷ 2.205 = Weight (in kilograms) Any conversions of units should be documented in the source documents.	Added language for clarity and to provide guidance on conversion of units.
9.10.9 Echocardiogram	An echocardiogram will be recorded as indicated in Table 4 to determine patient eligibility. The echocardiogram may be performed during the Screening Period, or an historical echocardiogram may be used if it was performed within 6 months prior to Day 1.	Added language for clarity.
9.10.10. Vital Sign Measurements	Vital sign measurements include the patient's pulse rate (beats/minute taken for at least 15 seconds), respiration rate, blood pressure, and body temperature. Vital sign measurements should be taken as indicated in Table 4. Blood pressure should be taken after the patient has rested in a sitting position for at least 5 minutes.	Updated to match the Schedule of Assessments, Table 4.

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	The same arm (usually the non-dominant arm) and the appropriate size cuff should be used for each measurement. For specific guidance related to blood pressure measurement, please see the Study Reference Manual. ~~Vital sign measurements should be taken as indicated in Table 4.~~	
9.10.11. Comprehensive Physical Examination & Targeted Physical Examination	A comprehensive physical examination must be performed by a physician, physician assistant, or registered nurse practitioner as indicated in Table 4 and as documented within the ~~table footnotes~~ medical record. The comprehensive physical examination must include the following organ or body system assessments: head, eyes, ears, nose, throat, musculoskeletal, cardiovascular, lymphatic, respiratory, abdomen, skin, extremities, and neurological. Assessments of any specific signs or symptoms reported by the patient must also be performed and documented along with any other findings of note. Clinically significant findings at Screening must be addressed in medical history, (i.e., findings should be attributable to a diagnosis recorded in medical history). Following the examination at Screening, new or changed physical examination findings meeting the definition of an 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. ~~A targeted~~ Targeted physical ~~examination (~~examinations are symptom-directed~~) should~~ examinations and involve the organ system(s) associated with the symptoms exhibited or reported. Targeted physical examinations are to be performed ~~as needed~~ at visits indicated in Table 4.	Clarification of what is required for a targeted physical examination.
9.10.12 Pregnancy Test	WOCBP (see Section 9.8) will complete a pregnancy test as indicated in Table 4, or at any time if pregnancy is suspected. Negative test results are required on Day 1 before study drug administration. ~~Any patient who becomes pregnant during the study must discontinue taking study drug immediately.~~ 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.	Added language for clarity, removed language not specifically relevant to the administration of pregnancy tests.
9.10.13 Study Drug Administration	For dose levels up to 20 mg, patients should self-administer one capsule orally once a day beginning on Day 1 (in clinic) through the end of the ~~study~~ Treatment Period, as indicated in Table 4. Patients who dose escalate to 30 mg should administer two capsules orally once a day. Each dose of study drug should be administered at approximately the same time each day. Study drug administration ~~(IP)~~ should be recorded in a patient diary through Week 100. ~~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.~~	Updated for clarity.

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9.10.14. Study Drug Dispensation and Collection	Study drug will be dispensed to the patient and collected from the patient as indicated in Table 4. The patient will be dispensed ~~one~~ the appropriate number of treatment kits at each timepoint: Day 1, Week 2, Week 4, Week 6 ~~(only if baseline ACR > 300 mg/g), and,~~ Week 8, ~~Three treatment kits will be dispensed at,~~ Week 12, Week 24, Week 36, Week 48, Week 52, Week 64, Week 76, and Week 88 ~~but,~~ If the patient is provided more than one kit, only one treatment kit should be opened at a time. Dispensed treatment kits from each visit (including unscheduled visits) should be returned to the site for collection at the subsequent visit. If the appropriate number of treatment kits (e.g., a 3-month supply) cannot be dispensed as outlined in Table 4, a partial supply may be provided to the patient. The remainder may be provided separately to the patient. Every effort should be made to avoid interruptions in dosing.	Updated to reflect the removal of the Week 48 to Week 52 off-treatment period and clarify the dispensation process.
9.10.16 Adverse Event Collection	~~AEs should be reported from the time of the first dose through 30 days after the last dose (or the End of Study visit, whichever is earlier).~~ See Section 11 for more detail regarding adverse events.	Added reference to more relevant section.
9.10.17 Kidney Ultrasound	Kidney ultrasound (historical or an ultrasound performed at Screen A) may be used to diagnose ADPKD~~and to assess for eligibility based on the Modified Pei-Ravine Criteria.~~ Patients with prior diagnosis of ADPKD will not have a kidney ultrasound performed as part of the study but must provide documentation of ADPKD diagnosis for eligibility.	Revised for clarity.

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9.10.18.1 eGFR	The equation used to calculate eGFR during the Screening Period is based on the patient's age at the time of consent/assent. The equation used to calculate eGFR for each patient throughout the study will be based on the patient's age at time of randomization. For Adults (≥ 18 years ≥ 70 years), eGFR will be calculated by a central laboratory using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation: $eGFR\ (mL/min/1.73\ m^2) = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$ For Adolescents (≥12 and < 18 years), eGFR will be calculated by a central laboratory using the Bedside Schwartz equation: $eGFR\ (mL/min/1.73\ m^2) = (0.41 \times \text{Height in cm}) / S_{cr}$ Where S_{cr} is serum creatinine (mg/dL), κ is 0.7 for females or 0.9 for males, and α is -0.329 for females or -0.411 for males. Min indicates the minimum of S_{cr}/κ or 1 and max indicates the maximum of S_{cr}/κ or 1. Age indicates age at time of lab collection. The eGFR values collected at Screen A and Screen B visits will be averaged to determine eligibility. The two eGFR values used to determine eligibility must have a percent difference ≤ 25%, as determined by the following calculation: Percent Difference = |X-Y| / ((X+Y)/2) *X=1st eGFR value (Screen A)* *Y=2nd eGFR value (Screen B)* *|X-Y|=absolute value of the difference between the two eGFR values* ~~The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation will be used:~~ In the absence of any clinically significant event or other medical conditions, the investigator should consider re-testing eGFR if the most recent value is significantly different from the prior value.	Added clarification on calculation of Screening eGFR values used for eligibility determination. Added formulas used for calculation of adult and adolescent eGFR values. Added language to encourage sites to consider re-testing eGFR if values are significantly different from prior values with no corresponding clinically significant event.

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9.10.22 Coagulation	Samples will be collected for the following coagulation assessments as indicated in ~~Table 4:Prothrombin Time (PT), and International Normalized Ratio (INR)~~Table 4: Prothrombin Time (PT) and International Normalized Ratio (INR). The coagulation assessments were added to the schedule of assessments through a protocol amendment. Sites should collect these samples from patients once the central laboratory kits and database enable collection. Until such time the site can collect this test, failure to collect it is not considered a protocol deviation.	Updated for clarity
9.10.23 Lipid Panel	The lipid panel was added to the schedule of assessments through a protocol amendment. Sites should collect these samples from patients once the central laboratory kits and database enable collection. Until such time the site can collect this test, failure to collect it is not considered a protocol deviation.	Updated for clarity
9.10.24 SARS-CoV-2 Antibody Testing	The SARS-CoV-2 antibody testing was added to the schedule of assessments through a protocol amendment. Sites should collect these samples from patients once the central laboratory kits and database enable collection. Until such time the site can collect this test, failure to collect it is not considered a protocol deviation.	Updated for clarity
[redacted]	[redacted]	[redacted]
9.10.32 Pharmacokinetics (PK) Blood Samples	Blood samples for determination of plasma bardoxolone methyl and potential metabolite concentrations will be drawn as indicated in Table 4. Patients must ~~be instructed to not take their study drug prior to coming to the clinic for visits when PK samples will be collected. Patients will be asked by site personnel to~~ provide the time of their last two ~~administrations~~ doses of study drug ~~prior to the~~ PK 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.~~ Central Laboratory Manual. 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	Updated the language for overall clarity. Provided specific detailed guidance for Week 12 PK, for Week 100 PK, and for PK assessments in the Off-Treatment Period (Week 103, 104, 108)

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	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. Patients who have discontinued study drug should not complete PK procedures. Week 12 PK If sites or patients are unable to perform the required PK assessments at the Week 12 visit, these PK assessments may be collected at Week 24, Week 36, or Week 48. Patients must refrain from taking study drug prior to coming to the clinic for the Week 12 visit, as patients will administer study drug in-clinic as instructed by the site. Patients must provide the time and date of the two most recent doses of study drug, prior to the blood samples being collected. Sites should obtain the 0-hour (pre-dose) PK sample, then instruct the patient to administer study drug. Blood samples for PK analysis should then be drawn at 2 and 4 hours post dose administration. Week 100 PK Patients must be instructed to refrain from taking study drug prior to coming to the clinic for the Week 100 visit, as patients will administer study drug in-clinic as instructed by the site. Patients must provide the time and date of the two most recent doses of study drug, prior to the blood samples being collected. Patients will have blood drawn at a single timepoint (i.e., pre-dose) for PK analysis at this visit. Sites should obtain the 0-hour (pre-dose) PK sample, then instruct the patient to administer the final dose of study drug in-clinic. Week 103, Week 104B, and Week 108B PK These PK assessments occur during the Off Treatment Period, so no study drug administration is associated with these assessments. Patients will have blood drawn at a single timepoint for PK analysis at this visit.	

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9.10.33 Ambulatory Blood Pressure Monitoring	For adult patients, Ambulatory Blood Pressure Monitoring (ABPM) is an optional sub-study conducted at the timepoints specified in Table 4. To participate, patients must have a baseline ABPM assessment. The baseline assessment must occur during the screening period, ideally 2-3 days prior to Day 1. The additional assessments occur at the following time points: Week 12, Week 48, and between Weeks 88 and 100 (prior to the patient's last dose of study drug). Participation in the ABPM sub-study is optional; however, patients should be encouraged to participate, and use of home health nurses/visits is strongly encouraged, to minimize the burden on the patient and to maximize participation. To ensure a sufficient volume of ABPM data, the Sponsor may halt enrollment of patients not participating in the ABPM sub-study. Participation will be monitored closely as overall enrollment progresses, and the Sponsor will update sites on progress toward achieving sufficient ABPM participation. A Sponsor-provided device will be placed on the patient by the study team, and the patient must wear the device for approximately 24 hours The addition of ABPM to the schedule of assessments occurred through a protocol amendment, and site and patient participation will be offered, once available. Upon completion of the 24-hour period, the site will collect the device from the patient and ABPM data will be sent to the central vendor to determine if the 24-hour recording passes the validity criteria. The criteria used to define a valid ABPM session for sites to determine the need for a repeat 24-hour session, if possible, are: • At least 70% of planned inflations are successful during the overall recording session; • At least 18 hours of analyzable data, and; • Not more than two consecutive hours of missing data. The addition of ABPM to the schedule of assessments occurred through a protocol amendment, and site and patient participation will be offered, once available.	Added optional ABPM sub-study to assess the impact of study drug on blood pressure. Included guidance to sites on who is eligible, required timepoints, etc.

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9.11.1 Dose Escalation Period	The first 8 weeks of the trial require intense safety monitoring of patients as they progress through the dose-escalation period of the study. When in-person visits are not be feasible, patients who are in the dose escalation period of the study should remain on their current study drug dose. The dose at the last in-person visit, if not the goal dose, will be considered the maximum dose until completion of dose-escalation can be safely resumed (see Section 9.11.5). Protocol specified in-clinic follow-up visits, for safety/tolerability, must be completed where possible. Required assessments for patients who are unable to have an in-person visit are described in Appendix 1 Section 4.	Added language for clarity regarding how to handle dose escalation when visits are missed.
9.11.2 Week 8 – 12 Visits	Patients in the maintenance period of the trial who have completed dose escalation and who have not reached the Week 12 time point must be assessed at Week 12 by conducting an in-person visit, per protocol. Patients who are unable to return to the clinic/site for a scheduled Week 12 follow-up visit should remain on their current study drug dose and have remote assessments completed to evaluate assess safety/tolerability. These remote assessments may be conducted as described in Appendix 1 Section 4.	Added language for clarity regarding how to handle dose escalation when visits are missed.
9.11.3 Post-Week 12 Visits	Patients who have completed dose escalation and who have completed the Week 12 Visit must be assessed at their next scheduled visit (Week 24). Patients who will be unable to return to the clinic/site for scheduled follow-up visits should remain on their current study drug dose and complete remote assessments to evaluate safety/tolerability until in-clinic visits can be resumed (see Section 9.11.5). These remote assessments may be conducted as described in Appendix 1 Section 4.	Added language for clarity regarding how to handle dose escalation when visits are missed.
9.11.4 Dose De-Escalation and Interruption for Missed Safety and Laboratory Assessments	If no in-clinic visit is completed and remote assessments/laboratory samples cannot be collected within the per protocol allowed time window for that visit, the study drug dose must be de-escalated to the previous dose within 6 days of the protocol visit window. For patients on 5 mg, the lowest dose, the dose may be maintained, and no de-escalation is required. All efforts should then be made to collect laboratory samples. However, if laboratory samples cannot be collected within 14 days from the date of dose de-escalation (for visits through Week 12) and within 28 days (for visits beyond Week 12), 5 mg study drug must be continued until safety lab values can be evaluated and it is deemed appropriate to dose-escalate. Section 9.11.5 describes the procedure for resuming and dose-escalating study drug following drug interruption.	Added language for clarity regarding how to handle dose escalation and dosing when visits are missed.

<table>
<tr><th>Section</th><th>Version 6</th><th>Rationale</th></tr>
<tr><td>9.11.5 Resuming or Dose Escalating Study Drug After Interruption or Changes</td><td>Patients who interrupt study drug due to a positive COVID-19 test may resume study drug without an in-clinic visit, at the investigator's discretion, of COVID-19 symptoms are mild.

When the investigator deems it is safe for the patient to return to the site for an in-person visit, the investigator should conduct an evaluation to determine whether the patient is still eligible to receive study drug and to determine the appropriate dose. This should include a confirmation that the reason for interruption was not a per protocol specified reason and that the patient's circumstances have not changed in a manner that would prohibit administration of the investigational drug (e.g., the patient is now taking an excluded medication). Once the investigator determines study drug administration is appropriate, dosing may proceed as recommended in the table below.

<table><tr><th>Study Drug Status</th><th>Dosing Recommendation</th></tr><tr><td>Study drug temporarily discontinued for any reason (e.g., COVID-19, delays in obtaining safety lab, AEs)</td><td>Resume study drug at last administered dose</td></tr><tr><td>Study drug dose not escalated as required per COVID-19 mitigation plan</td><td>Continue last administered dose; consider escalating dose, if appropriate</td></tr><tr><td>Study drug de-escalated for any reason (e.g., due to delays in obtaining safety labs, AEs)</td><td>Continue last administered dose; consider escalating dose, if appropriate</td></tr></table>
If the patient is not at the target dose, dose escalation to a higher dose is permitted. Patients who dose escalate must have a telephone call 1 week after dose escalation and an office visit (or unscheduled visit, if necessary) 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 9.1 of the protocol. Once the target dose has been reached and 2-week follow-up completed, the Schedule of Assessments may be resumed.</td><td>Added language to permit patients who have a short term interruption due to mild COVID-19 to resume IP without an in-clinic visit, at the PI's discretion.</td></tr>
<tr><td>10.2 Study Drug Packaging and Labeling</td><td>When applicable, a double-panel label will be presented on the treatment kit carton containing this and other information ~~as well~~. Additionally, labeling, in the relevant local languages for ~~investigational medicinal product (IMP) for~~ study drug use and distribution in the EU shall adhere to current Eudralex, Volume 4 Annex 13 guidance and requirements.
In the event the investigational product is not packaged as intended or may not adhere to Current Good Manufacturing Practices (CGMP), a complaint should be filed with the Sponsor, ideally through the site's CRA. Guidance on filing IMP complaints is available in the Study Reference Manual, and attention should be given to ensure the patient number is not submitted within the complaint documentation.</td><td>Updated to provide guidance on IP complaint process.</td></tr>
</table>

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10.3 Study Drug Storage	If the investigational product is stored outside of the designated conditions, a temperature excursion notification should be submitted to the Sponsor for review and approval for use of the affected IP. Guidance on filing temperature excursions is available in the Study Reference Manual.	Updated to provide guidance on IP temperature excursion process.
10.4 Study Drug Administration	Please refer to Section 9.10.13 for details on study drug administration. ~~Clear~~ It is the responsibility of the investigator or designee to provide clear instructions ~~will be provided~~ to the patient regarding the number and type of capsules to be ingested at each study drug administration time point listed in Table 4. Patients must be instructed to continue taking study drug once daily ~~up through their Week 48 visit and from Week 52~~ through Week 100 unless: (1) the patient has been otherwise instructed by the investigator or (2) the patient has been formally discontinued from study treatment.	Updated due to remove of off-treatment period in Year 1.
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 investigator or designee will maintain a record of all study drug received, dispensed, and returned. The number of capsules returned at each visit will be recorded by the site for each bottle in the kit. The site will make these records available for Sponsor or designee review.	Added language to clarify required records and to ensure records are made available to Sponsor.
10.6 Study Drug Handling and Disposal	At any time during the ~~conclusion~~ conduct 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. No study drug shall be destroyed by the clinical site unless agreed upon in writing by the Sponsor. Documentation of study drug disposition will be retained with the investigator. Refer to the IP Handling Manual for detailed instructions on study drug handling and disposal.	Added language to clarify if and when study drug may be destroyed.
11.1 Safety Parameters	Safety parameters include vital sign measurements, ECG results, AEs, SAEs, weight, and laboratory test results ~~(clinical chemistry, hematology, urinalysis and microscopy).~~	Removed specific lab listings, as these are covered broadly by laboratory test results.

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11.2.1.1. Adverse Event	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~~ 30 days following administration of the last dose of study drug) as indicated in Table 4 must be reported, regardless of their relationship to study drug or their clinical significance. ~~For patients who discontinue study drug early, AEs should be reported through 30 days following the date of last dose of study drug.~~ SAEs, if considered related to study drug, can be reported at any time during the study duration. In addition, as noted in Section 11.2.1.2, death, initiation of dialysis, or transplant should be reported through Week 112, on the appropriate eCRF.	Adjusted the AE reporting timeframe to continue from the time of first dose through 30 days following administration of the last dose, for all patients. Clarified that related SAEs can be reported through Week 112 (approximated 12 weeks following last dose of IP).
11.2.1.2. Serious Adverse Event	The investigator is responsible for reporting to Reata or designee all AEs and SAEs that are observed or reported by the patient during the study (from the time of administration of the first dose of study drug until the final visit indicated in Table 4, as appropriate), including events resulting from protocol-associated procedures as defined in relevant legislation, and regardless of their relationship to study drug or their clinical significance. For patients who discontinue study drug early, SAEs should be reported through 30 days following the date of last dose of study drug. ~~with the exception of~~ SAEs, if considered related to study drug, should be reported at any time during the study. In addition, death, ~~kidney transplant, or~~ initiation of dialysis, or transplant ~~which~~ should be reported through Week ~~104~~ 112, on the appropriate eCRF (see Section 11.7). The Sponsor may request additional information from the investigator to ensure the timely completion of accurate safety reports.	Updated visit number based on added Week 112 visit.
11.6 Recording Adverse Events	~~While an AE is ongoing, changes~~ For guidance on how to handle AEs that change in ~~the~~ severity (e.g., worsening ~~and~~ or improving~~) should be noted in the source documents, but when documenting the AE, only the total duration and greatest severity should be recorded in~~), see the eCRF~~. AEs characterized as intermittent require documentation of onset and duration.~~ Completion Guidelines. 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, within normal limits, or stabilization). All other AEs will be followed through the ~~final visit indicated in Table 4, as appropriate~~ 30 days after the last dose of study drug.	Added language to direct sites to the eCRF completion guidelines for instruction on how to record AEs that change in severity.

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11.7 Reporting Serious Adverse Events	To report the SAE, fax or email the completed SAE form t [redacted] within 24 hours of awareness: Table ~~8~~7: SAE Reporting Contact Information Within 24 hours of receipt of new information, the updated follow-up SAE form, along with any supporting documentation (e.g., patient discharge summary or autopsy reports), should be faxed or emailed [redacted].	Updated table numbers.
12.1 Sample Size	With ~~550~~ 850 patients enrolled, the study will have approximately 80% power to detect a difference between the two treatment groups in change from baseline eGFR of ~~3.1~~ 2.3 mL/min/1.73 m^2. The power calculation was based on a 2-sample t-test as an estimate for the planned ANCOVA analysis and assumes the following: - Overall two-sided Type I error rate total of 0.05~~; 0.025 allocated to primary endpoint and 0.025 allocated to the key secondary endpoint~~; - ~~Proportion of~~ patients ~~with missing off-treatment data not to exceed 15%;~~ - Standard deviation of change from baseline in eGFR of ~~11~~ 12 mL/min/1.73 m^2; - Analyses are based on the intent-to-treat (ITT) population; - Missing data ~~are not imputed (sensitivity analyses, including a tipping point analysis, will be performed to assess the impact of missing data).~~ will be imputed using multiple imputation.	Update in primary endpoint that impacts the sample size since the W108 value will be used for endpoint analysis, regardless of how long a patient has been off treatment. A dilution in the difference between treatment groups at Week 108 is expected due to contribution of early treatment discontinuation patients who received a shortened treatment duration and have a longer untreated period associated with natural disease progression. Therefore, the expected treatment effect is reduced from 3.1 to 2.3 mL/min/1.73m^2.

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		Additionally, the assumed variability was increased based on observed variability at Week 104 in the completed 1603 Phase 3 study and a longer off-treatment period for the primary endpoint. The sample size was increased from 550 to 850 to account for the change in expected treatment effect and increased variability.
12.2.3 Safety Variables	The safety variables include results of laboratory ~~test results (clinical chemistry, hematology, urinalysis and microscopy) ,~~testing, vital sign measurements, ECG results, weight, [redacted], AEs, and SAEs.	Removed unnecessary language, broadly covered by laboratory testing.
12.3.1. Analysis of Efficacy	The ITT population, which includes all patients randomized within each cohort, will be used as the population for assessment of the efficacy endpoints. This includes patients on tolvaptan who have already enrolled under Version 2 of the protocol. Analysis of covariance (ANCOVA) will be used to analyze the primary ~~and key secondary~~ efficacy endpoints of change from baseline in off-treatment eGFR. The model will include change from baseline in eGFR as the dependent variable, treatment group as fixed effect, and baseline eGFR as continuous covariate. Other covariates may be specified in the SAP. The off-treatment endpoints assess the preserved drug benefit relative to placebo following withdrawal of treatment; therefore, analyses of these endpoints do not include eGFR values collected during treatment. ~~Missing data are not imputed.~~ Sensitivity analyses, including a tipping point analysis, will be performed to assess the impact of missing data.	Clarification
13.1 Study Monitoring	In case that study sites are closed for any visitors and monitors over a certain period of time during the COVID-19 pandemic, a risk-based approach to monitoring will be taken, focusing on certain sites, certain	Added language to clarify adjustments in monitoring due to

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	data points and certain processes that are critical to ensure the rights, safety and well-being of trial participants and the integrity of the trial (and trial data). The results of adjusted monitoring/review measures and their impact will be reported to the Sponsor in monitoring reports and in the clinical study report, where applicable. Adjusting monitoring activities may include a combination of on-site and off-site monitoring, where permitted by local regulations. Remote source data verification may also be taken into consideration, where permitted by local regulations.	COVID-19 impacts on site operations.
14.4 Investigational Documentation	• The IRB- or EC-approved informed consent~~;~~ (and assent, if applicable), 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;	Updated for inclusion of assent.
15.1 Institutional Review Board (IRB) or Ethics Committee (EC) Review	The protocol and the proposed informed consent form (and assent, if applicable) 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 (and assent, if appliable) 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.	Updated for inclusion of assent.
15.3 Written Informed Consent	For adolescent patients, informed consent will be obtained from the parent(s) or legal guardian in accordance with regional laws or regulations. In addition, dependent upon the patient's age and IRBs, IEC, and/or local legal requirements, assent of the patient must also be obtained. Adolescent patients may be asked to personally sign and date either a separately designed, written assent form, or the written informed consent.	Updated for inclusion of assent.
15.6 Protocol Deviations	Deviations will be reported, evaluated, and discussed according to the Protocol Deviation Plan and in the final study report. All protocol deviations due to the impacts of COVID-19 will be identified and documented accordingly by the site and the Sponsor. When visits are completed remotely (due to COVID-19 or other reasons), sites should ensure the completion of at least those assessments listed in Appendix 1 Section 4. Where these study procedures are completed remotely, any additional study procedures that cannot be completed will be	Added language from the COVID-19 Appendix within the Protocol.

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	noted as missing and will not be considered as a protocol deviation. The failure to complete the minimally required procedures outlined in Appendix 1 Section 4, will be considered a protocol deviation.	
Appendix 1, Section 2: COVID-19 Infected Patients and Study Drug Use	If a patient enrolled in the study tests positive for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), ~~the causative agent of COVID-19, IP~~ study drug must be temporarily discontinued ~~until~~ The Sponsor must be notified immediately for additional guidance. Study drug may be resumed when the patient no longer presents an active infection, (defined as resolution of symptoms or a negative SARS-CoV-2 test), as assessed by the Investigator and/or the patient's physician(s). ~~The Sponsor must be notified immediately for additional guidance~~ If COVID-19 symptoms persist (e.g., loss of taste or smell), the patient should be encouraged to repeat SARS-CoV-2 testing in order to minimize the duration of study drug interruption. Instructions on resuming study drug following a positive SARS-CoV-2 test result COVID-19 infection are provided in Appendix 1 Section 5.5.	Added emphasis that Sponsor must be contacted immediately for guidance. Clarified when study drug may be resumed. Added language to permit sites to re-test a patient whose symptoms persist, to determine whether to re-start study drug based on the negative test, rather than resolution of all symptoms.
Appendix 1, Section 5.1: Dose Escalation Period	~~The first 8 weeks of the trial require intense safety monitoring of patients as they progress through the dose escalation period of the study. Because in person clinical visits may not be feasible, patients who are in the dose escalation period of the study should remain on their current IP dose. The dose at the last in person clinic visit, if not the goal dose, will be considered the maximum dose until completion of dose escalation can be safely resumed (see Appendix 1 Section 5.5).~~ ~~Protocol specified in clinic follow up visits, for safety/tolerability, must be completed where possible. Required assessments for patients who are unable to have an in person visit are described in Appendix 1 Section 4.~~ Refer to Section 9.11.1.	Section moved.
Appendix 1, Section 5.2: Week 8-12 Visits	~~Patients in the maintenance period of the trial who have completed dose escalation and who have not reached the Week 12 time point must be assessed at Week 12 by conducting an in clinic visit, per protocol.~~	Section moved.

Section	Version 6	Rationale
	~~Patients who are unable to return to the clinic/site for a scheduled Week 12 follow-up visit should remain on their current IP dose and have remote assessments completed to evaluate assess safety/tolerability.~~ Refer to Section 9.11.2.	
Appendix 1, Section 5.3: Post-Week 12 Visits	~~Patients who have completed dose escalation and who have completed the Week 12 Visit must be assessed at their next scheduled visit (Week 24). Patients who will be unable to return to the clinic/site for scheduled follow-up visits should remain on their current IP dose and complete remote assessments to evaluate safety/tolerability until in-clinic visits can be resumed (see Appendix 1 Section 5.5). These remote assessments may be conducted as described in Appendix 1 Section4.~~ Refer to Section 9.11.3.	Section moved.
Appendix 1, Section 5.4: Dose Escalation and Interruption for Missed Safety and Laboratory	~~If no in-clinic visit is completed and remote assessments/laboratory samples cannot be collected within the per protocol allowed time window for that visit, the IP dose must be de-escalated to the previous dose within 6 days of the protocol visit window. For patients on 5 mg, the lowest dose, the dose may be maintained and no de-escalation is required. All efforts should then be made to collect laboratory samples. However, if laboratory samples cannot be collected within 14 days from the date of dose de-escalation (for visits through Week 12) and within 28 days (for visits beyond Week 12), IP must be temporarily discontinued until safety lab values can be evaluated and it is deemed appropriate to restart. Appendix 1 Section 5.5 describes the procedure for resuming and dose-escalating IP following drug interruption.~~ Refer to Section 9.11.4.	Section moved.
Appendix 1, Section 5.5: Resuming or Dose-Escalating Study Drug after Interruption or Changes	~~When the investigator deems it is safe for the patient to return to the site for an in-person visit, the investigator should conduct an evaluation to determine whether the patient is still eligible to receive IP and to determine the appropriate dose. This should include a confirmation that the reason for discontinuation was not a per protocol specified reason and that the patient's circumstances have not changed in a manner that would prohibit administration of the investigational drug (e.g. the patient is now taking an excluded medication). Once the investigator determines IP administration is appropriate, dosing may proceed as recommended in the table below.~~ ~~**IP Status** | **Dosing Recommendation**~~	Section moved.

Section	Version 6	Rationale
	~~IP temporarily discontinued for any reason (e.g. COVID-19, delays in obtaining safety lab, AEs)~~ — ~~Resume IP at last administered dose~~ ~~IP dose not escalated as required per COVID-19 mitigation plan~~ — ~~Continue last administered dose; consider escalating dose, if appropriate~~ ~~IP de-escalated for any reason (e.g. due to delays in obtaining safety labs, AEs)~~ — ~~Continue last administered dose; consider escalating dose, if appropriate~~ ~~If the patient is not at the target dose, dose escalation to a higher dose is permitted. Patients who dose escalate must have a telephone call 1 week after dose escalation and an office visit (or unscheduled visit, if necessary) 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 of the protocol. Once the target dose has been reached and 2 week follow up completed, the Schedule of Assessments may be resumed.~~ Refer to Section 9.11.5.	
Appendix 1, Section 6: Deviations	~~Any study procedures that cannot be conducted remotely will be noted as missing. All deviations due to the impacts of COVID-19 will be identified and documented accordingly by the site and the Sponsor. The failure to complete a protocol visit will not be considered as a reason for study discontinuation and will not be considered as a major deviation. Deviations will be reported, evaluated, and discussed according to the Protocol Deviation Plan and in the final study report.~~ Refer to Section 15.6.	Section moved.
Appendix 1, Section 7: Monitoring	~~In case that study sites are closed for any visitors and monitors over a certain period of time during the COVID-19 pandemic a risk-based approach to monitoring will be taken, focusing on certain sites, certain data points and certain processes that are critical to ensure the rights, safety and well-being of trial participants and the integrity of the trial (and trial data). The results of adjusted monitoring/review measures and their impact will be reported to the Sponsor in monitoring reports and in the clinical study report, where applicable. Adjusting monitoring activities may include a combination of on-site and off-site monitoring. Remote source data verification may also be taken into consideration.~~ Refer to Section 13.1.	Section moved.

AMENDMENT CHANGE DOCUMENT
CLINICAL STUDY PROTOCOL 402-C-1808

Study Title: A Phase 3 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with Autosomal Dominant Polycystic Kidney Disease

Protocol History

Version 01	12 December 2018
Version 02	4 March 2019
Version 03	16 July 2019
Version 04	25 June 2020
Version 05	25 February 2021

Confidentiality Statement

SUMMARY OF CHANGES

The following document outlines the changes that have been made to Version 4 to produce the text of Version 5. Additionally, the following points are provided:

- New text that is added is marked with an underscore; text that has been deleted is marked with a ~~strikethrough~~.
- The changes made in the body of the protocol are reflected in the synopsis; the corresponding changes made in the synopsis are not described.
- Grammatical corrections and minor editorial changes are not described.
- Section numbers refer to the numbers in the new version of the protocol.

Section	Version 5	Rationale
Table 1: Emergency Contact Information	[redacted]	Updated contact information for [redacted]
Section 2: Synopsis	**Study Period:** ~~3.5~~4.75 years Estimated date first patient enrolled: ~~June~~May 2019 Estimated date last patient completed: ~~December 2023~~February 2024	Updated study period, Estimated first patient enrolled, and Estimated date last patient completed due to increased sample size

Section	Version 5	Rationale
Section 2: Synopsis	**Methodology:** This international, multi-center, randomized, double-bind, placebo-controlled, phase 3 trial will study the safety, tolerability, and efficacy of bardoxolone methyl in qualified patients with ADPKD. Approximately ~~300~~550 will be enrolled. ~~The primary efficacy endpoint will be analyzed after all patients have completed their Week 52 visit. The key secondary e~~Efficacy endpoint~~s~~ will be analyzed after all patients have completed their Week 104 visit.	Increase in sample size is based on the change in assumption for standard deviation (SD) for eGFR from SD=8 to SD=12. The change in assumption for increase in SD is based on the eGFR variability observed in a recently completed 402-C-1603 Phase 3 study where eGFR change from baseline was used as an efficacy endpoint over 2 years, a design similar to the current study.
Section 2: Synopsis	**Number of patients (planned):** Approximately ~~300~~550 patients will be enrolled.	Updated sample size

Section	Version 5	Rationale
Section 2: Synopsis	**Diagnosis and main criteria for inclusion:** 3. Screening eGFR (the two values collected at Screen A and B) must: a. Have a percent difference ≤ 25%; b. Have an average ≥ 30 to ≤ 90 mL/min/1.73 m^2 for patients 18 to 55 years or ≥ 30 to ≤ 44 mL/min/1.73 m^2 for patients 56 to 70 years; c. According to the medical monitor, support ADPKD disease progression (i.e., eGFR decline of ≥ 2.0 mL/min/1.73 m^2 per year) for patients with either screening eGFR ≥ 60 to ≤ 90 mL/min/1.73 m^2 or age 56 to 70 years ~~3. Screening eGFR (average Screen A and Screen B eGFR values) ≥ 30 to ≤ 90 mL/min/1.73 m^2 (18 to 55 years) or ≥ 30 to ≤ 44 mL/min/1.73 m^2 (56 to 70 years):~~ ~~a. Medical monitor approval is required to confirm ADPKD progression (i.e. eGFR decline of ≥ 2.0 mL/min/1.73 m^2 or age 56 to 70 years, must have evidence of ADPKD progression (i.e. eGFR decline of ≥ 2.0 mL/min/1.73 m^2 per year, based on historical eGFR data and medical monitor discretion);~~ ~~b. The two eGFR values collected at Screen A and Screen B visits used to determine eligibility must have a percent difference ≤ 25%;~~	Updated language for clarity for inclusion criterion 3
Section 2: Synopsis	**Major Exclusion Criteria** 22. Coronavirus disease 2019 (COVID-19) diagnosis within 6 months to Randomization, with accompanying symptoms, or even required COVID-19 related hospitalization.	Addition of exclusion criterion for COVID-19 diagnosis

Section	Version 5	Rationale
Section 2: Synopsis	**Statistical Methods:** Sample size: With ~~300~~550 patients enrolled, the study will have approximately 80% power to detect a difference between the two treatment groups in change from baseline eGFR of 3.1 mL/min/1.73 m^2. The power calculation was based on a 2-sample t-test as an estimate for the planned ANCOVA analysis and assumes the following: • Overall two-sided Type I error rate of 0.05; ~~0.025 allocated to the primary endpoint and 0.025 allocated to the key secondary endpoints;~~ • Proportion of patients with missing off-treatment data not to exceed 15%; • Standard deviation of change from baseline in eGFR of ~~8~~11 mL/min/1.73 m^2; • Analyses are based on the intent-to-treat (ITT) population; • Missing data are not imputed (sensitivity analyses, including a tipping point analysis, will be performed to assess the impact of missing data).	The change in assumption for increase in SD is based on the eGFR variability observed in a recently completed 402-C-1603 phase 3 study where eGFR change from baseline was used as an efficacy endpoint over 2 years, a design similar to the current study.
Section 4: List of Abbreviations and Definitions of Terms	IP: Investigational product ITT: Intent-to-treat	Updated list of abbreviations

Section	Version 5	Rationale
Section 5.1: Clinical Experience with Bardoxolone Methyl	Overall, bardoxolone methyl has been tested in multiple ~~CKD~~ studies enrolling over 3,000 patients, and over ~~3,000~~2,500 individuals have been exposed to bardoxolone methyl.	Corrected 3,000 to 2,500 the correct approximation of patients exposed to bardoxolone methyl
Section 5.1.2.2: Transaminase and Gamma-glutamyl Transpeptide (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.	Updated information for clarity
Section 7.1: Overall Study Design	This international, multi-center, randomized, double-blind, placebo-controlled phase 3 trial will study the safety, tolerability, and efficacy of bardoxolone methyl in qualified patients with ADPKD. Approximately ~~300~~ 550 patients will be enrolled.	Updated sample size

Section	Version 5	Rationale
Section 7.1: Overall Study Design	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, 12, 24, 36, 48, 52, 64, 76, 88, 100, and 104 and by telephone contact on Days 3, 10, 21, 31, 38, and 45. Patients will not receive study drug during a 4-week withdrawal period between Weeks 48 and 52. They will re-start treatment at Week 52 at the same dose they were ~~received~~ receiving at Week 48 and will continue study drug through Week 100. Patients will also be scheduled to be assessed at an in person follow-up visit at Week 104, four weeks after the end of treatment.	Updated language for clarity
Section 7.2: Number of Patients	Approximately ~~300~~550 patients will be enrolled.	Increased sample size
Section 7.3.1: Dose Escalation	Patients randomized to placebo will remain on placebo throughout the study, undergoing sham titration. Patients receiving bardoxolone methyl will start with once-daily dosing at 5 mg and will dose-escalate to 10 mg at Week 2, to 20 mg at Week 4, and then to 30 mg at Week 6 (only if baseline ACR > 300 mg/g) unless contraindicated clinically and approved by the medical monitor. Dose escalation may need to proceed more slowly if the patient experiences early elevations in ALT/AST over ULN, e.g. at Week 2 (see Section **9.1.2**). The dosing objective is to titrate patients to the maximum 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, 4, or 6 with the medical monitor. In cases where dose escalation is delayed or not achieved prior to Week 48, the investigator should consider dose escalation to goal dose after study drug is resumed in Week 52.	Clarification on dose escalation

Section	Version 5	Rationale
Section 7.3.3 Dose Interruption and Re-Challenge	In addition to dose-de-escalation and re-escalation, the study drug administration can be interrupted if clinically indicated. All efforts should be made to reinitiate drug after any duration following discontinuation. If patient discontinues study drug but continued to be followed in the study, drug rechallenge should be considered at any point including Year 2 of the study. All patients with study drug discontinuation should be discussed with medical monitor.	Addition of dose re-challenge instructions
Section 7.5: Schedule of Assessments (Table 4)	**Assessment** • Physical Exam: Removed at Weeks 1, 2, 4, 6, 8, 12, 24, 36, 48, 64, 76, and 88 • Targeted Physical Exam: Added at Weeks 1, 2, 4, 6, 8, 12, 24, 36, 48, 64, 76, and 88 • Coagulation Panel: Added at Day 1, Weeks 2, 4, 6, 8, 12, 24, 36, 48, 52(B), 64, 76, 88, 100 or End of Treatment, and 104(B) or Follow-Up(B) • Basic Lipid Panel: Added at Day 1, Week 52(B), Week 100 or End of Treatment, and Week 104(B) or Follow-up(B) • SARS-CoV-2 Antibody Test: Added at Week 52(A) and Week 104(B) or Follow-up(B)	Addition of targeted physical exams as a replacement for complete physical exams at certain timepoints due to complete physical exam not being required at all visits, addition of coagulation panel, lipid panel, and SARS-CoV-2 antibody testing for patient safety.

Section	Version 5	Rationale
Section 7.5: Schedule of Assessments (Table 4)	**Footnotes** [a]Total Screening period should not exceed ~~6~~3 months. [b]Screen B visit should be at least 1 day after Screen A and no more than 30 days prior to Day 1. [c]Day 1 should be~~is~~ the day of randomization and administration of the first dose. Where randomization in the RTSM must occur earlier than Day 1, the Day 1 visit must align with administration of the first dose. **On Day 1, all procedures must be performed before study drug administration.** ~~**The patient visit schedule is based on date of randomization.**~~ [h]Kidney ultrasound (historical or one obtained at Screen A) may be used to diagnosis ADPKD ~~**at Screen A**~~ for patients without prior ADPKD diagnosis. [k]Both Week 52 visits must be completed ~~21~~28 to ~~35~~36 days after the last dose. [l]Both Week 104 visits must be completed ~~21~~28 to ~~35~~36 days after the last dose in year 2.	Clarification (full rationale in associated protocol section)
Section 7.5: Schedule of Assessments (Table 4)	~~**EC = ethics committee**~~	Abbreviation removed

Section	Version 5	Rationale
Section 8.1: Patient Inclusion Criteria	3. Screening eGFR (the two values collected at Screen A and B) must: a. Have a percent difference ≤ 25%; b. Have an average ≥ 30 to ≤ 90 mL/min/1.73 m^2 for patients 18 to 55 years or ≥ 30 to ≤ 44 mL/min/1.73 m^2 for patients 56 to 70 years; c. According to the medical monitor, support ADPKD disease progression (i.e., eGFR decline of ≥ 2.0 mL/min/1.73 m^2 per year) for patients with either screening eGFR ≥ 60 to ≤ 90 mL/min/1.73 m^2 or age 56 to 70 years ~~3. Screening eGFR (average Screen A and Screen B eGFR values) ≥ 30 to ≤ 90 mL/min/1.73 m^2 (18 to 55 years) or ≥ 30 to ≤ 44 mL/min/1.73 m^2 (56 to 70 years):~~ ~~a. Medical monitor approval is required to confirm ADPKD progression (i.e. eGFR decline of ≥ 2.0 mL/min/1.73 m^2 or age 56 to 70 years, must have evidence of ADPKD progression (i.e. eGFR decline of ≥ 2.0 mL/min/1.73 m^2 per year, based on historical eGFR data and medical monitor discretion);~~ ~~b. The two eGFR values collected at Screen A and Screen B visits used to determine eligibility must have a percent difference ≤ 25%;~~	Updated information for clarity and numbering updated
Section 8.2: Patient Exclusion Criteria	22. Coronavirus 2019 (COVID-19) diagnosis within 6 months prior to Randomization, with accompanying symptoms, or even required COVID-19-related hospitalizations.	Added exclusion criterion for COVID-19 diagnosis

Section	Version 5	Rationale
Section 8.3: Screening Period	The screening period must not exceed ~~6~~3 months. The Screen B visit should be no more than 30 days prior to Day 1.	Shortened screening window to ensure stable clinical status from Screen A to Randomization
Section 8.5.1: Patient Study Drug Discontinuation Criteria	To minimize missing data, patients who are permanently discontinued from study drug should still continue with study follow-up, completing all study visits and undergoing all scheduled study assessments through Week 104, if possible. The collection of laboratory data and vital status (including ESKD status) through Week 104 is important for trial integrity, and data may be obtained through in-person clinic visits or through home health visits – AEs and SAEs should be collected for 30 days following the date of last dose.	Clarification of importance of patient data collection after study drug discontinuation
Section 8.5.1: Patient Study Drug Discontinuation Criteria	A patient who permanently discontinues treatment anytime prior to Week 100 will have an end of treatment visit as close as possible to the day of last dose. The patient will then complete both Follow-up A and Follow-up B visits within ~~21~~ 28 to ~~35~~ 36 days after last dose. Safety and clinical chemistry assessments, including a serum chemistry creatinine assessment for efficacy, will be performed at the end of treatment and follow-up visits. After the follow-up visits, the patient will continue with all assessments up to and including their scheduled Week 52 and Week 104 visits. AEs and SAEs should be reported for 30 days following the patient's last dose of IP.	Clarification of visit window and AE/SAE reporting

Section	Version 5	Rationale
Section 9.1.1: Management of Fluid Status	Laboratory data and rapid weight gain will also be used to monitor fluid status after randomization. Patients who experience a BNP > 100 pg/mL that represents a doubling (or more) of BNP levels from Day 1 should have an unscheduled telephone contact immediately (see section 9.10.15 for description of telephone contact). In addition, patients will be given a Sponsor-provided scale to use at home to collect and record ~~their~~ weights daily during the ~~first 8 weeks of the treatment period and weekly thereafter~~ study. Patients who experience a weight increase of three pounds (1.4 kilograms) in a day or five pounds (2.3 kilograms) or greater increase ~~in weight~~ within a week ~~since their Day 1 weight during the first 8 weeks~~ must have an unscheduled telephone contact immediately. Whether ~~due to~~prompted by BNP elevations or weight gain, if clinically important fluid retention is suspected, the patient must be instructed to stop taking their study medication immediately and be medically evaluated by the investigator or a local physician within 1 to 2 days. Investigators are encouraged to consider starting or increasing doses of diuretics (thiazides, loop diuretics) early after recognition of edema. This can be done concurrently with temporary drug discontinuation and re-initiation. Patients may not restart their study medication until the investigator has completed and documented an assessment of fluid overload. ~~Beyond Week 8, patients who experience a weight increase of five pounds (2.3 kilograms) or greater compared to Day 1 will be instructed to contact the clinic to assess the need for an unscheduled physical exam and laboratory assessment by the investigator. Study medication should not be discontinued unless clinically important fluid retention is suspected. If suspected, the patient must be instructed to stop taking their study medication immediately and be medically evaluated by the investigator or a local physician within 1 to 2 days.~~	Defined increases in weight over a shorter period (1 day or 1 week) is more clinically meaningful than changes in reference to the baseline weight, over a 2 year study period.

Section 9.1.2 Management of Elevated Transaminase Levels (ALT and/or AST)	Repeat testing every 72 to 96 hours until transaminase levels are below 3X the ULN for at least one week. Testing for patients not located near the investigator (such that it is not practical to return to the site at the required intervals) may be performed by a home health nurse using a central lab kit, or at a local lab and sent to the investigator and medical monitor for review ~~(by approval from the medical monitor).~~ Discontinue study drug administration temporarily and contact the medical monitor to discuss 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 study drug may be restarted with the Sponsor's approval after the following criteria are fulfilled: • Ultrasound of the hepatobiliary tree; • ALT and AST returned to < ULN; • TBL is within normal range; • Other relevant labs (e.g., albumin, INR, PT) are within normal range; • No clinical signs or symptoms of liver injury are present. Patients restarting study drug should start at the 5 mg dose level and dose titrate according to Section 7.3.2. The hepatobiliary tree must be visualized (e.g., ultrasound, magnetic resonance imaging [MRI]) and assessed if a patient meeting above discontinuation criteria discontinues taking study drug ~~secondary to elevated transaminase levels~~. Additional tests/studies may be warranted depending on the clinical presentation	Updated information and clarification for discontinuation of study drug due to transaminase elevation

Section	Version 5	Rationale
Section 9.1.4 Weight Loss	The investigator should evaluate a patient for unexplained weight loss of 7% or greater from the Day 1 weight. 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.	Update to weight loss parameters

Section	Version 5	Rationale
Section 9.1.9 End Stage Kidney Disease	Patients approaching end stage kidney disease (ESKD) should be closely monitored by the investigator to fully characterize their progression. For patients with eGFR ≤ 15.0 mL/min/1.73 m^2, initiate more frequent follow-up to closely monitor safety assessments (i.e., clinical chemistry (incl. eGFR), hematology, vital sign assessments (incl. weight), BNP and NT-proBNP). Similar frequent follow-up may also be implemented for patients with eGFR > 15.0 mL/min/1.73 m^2 who, in the investigator's opinion based on the anticipated progression of their disease, may be approaching ESKD. Patient follow-up should be completed in-person or through a home health visit where in-person visits are not feasible, at least once every 4 weeks (±2 weeks), until one of the following occurs: • Initiation of dialysis; • Receipt of transplant Two off-treatment serum creatinine assessments should be collected 2~~1~~8 to 3~~5~~6 days after last dose, and prior to initiation of dialysis or receipt of transplant. Upon initiation of dialysis, study drug should be temporarily discontinued. Because laboratory and vital sign assessments can be affected by receiving dialysis, those safety assessments should not be performed concurrently while a patient is receiving dialysis. Patients receiving dialysis should continue to be followed for vital status and SAEs by phone or in-person according to the protocol scheduled visits. Dialysis not lasting at least 12 weeks will be considered acute dialysis, and patients should be considered for re-initiation of study drug with medical monitor approval. Such patients should continue to undergo frequent follow-up (i.e., at least once every 4 weeks (± 2 weeks)) while eGFR ≤ 15.0 mL/min/1.73 m^2. Study drug may be re-started following acute dialysis, with medical monitor approval. Dialysis lasting at least 12 weeks will be confirmed as maintenance dialysis. Upon confirmation of maintenance dialysis, study drug should be permanently discontinued.	Clarification on the follow-up for ESKD

Section	Version 5	Rationale
Section 9.3.1 Excluded Medications	Concomitant use with strong and moderate CYP3A4 inhibitors is prohibited. If a strong or moderate CYP3A4 inhibitor is medically necessary, study drug ~~should~~must be temporarily discontinued. Concomitant study drug use with strong and moderate CYP3A4 inhibitors ~~should~~must be avoided ~~whenever possible,~~ and switching to an alternate agent should be considered. ~~When concomitant use of a moderate CYP3A4 inhibitor is unavoidable, patients should be carefully monitored and the study drug dose may be temporarily reduced or should be temporarily discontinued at the discretion of the investigator.~~ Concomitant use of strong CYP3A4 inducers if prohibited.	Clarification on the use of CYP3A4 concomitant medications
Section 9.3.2 Permitted Medications	Allowed concomitant medications include the following: • Antibiotics (for moderate and strong CYP3A4 inhibitors/inducers, see section 9.3.1); • Daily multivitamins or recommended daily supplements; • Other medications intended to manager concurrent diseases, as authorized by the treating physician; • Oral, implantable, or injective 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.	Clarification for permitted antibiotic use

Section	Version 5	Rationale
Section 9.4 Treatment Compliance	The investigator or his/her designated and qualified representatives will only dispense study drug to patients enrolled in the study in accordance with the protocol. Patients should administer study drug exactly as instructed by the site. Non-compliance is defined as taking less than 80% or more than 110% of expected study medication during any evaluation period (visit to visit). A lack of treatment compliance during any evaluation period (visit to visit) should be entered as a deviation. Patients should record in the patient diary all administered and missed doses of study drug. The reason for a missed dose should be recorded in the patient diary. A missed dose includes drug holidays and temporary study drug discontinuations. Patients will be asked to return all unused study drug (study drug bottles and any unused capsules). The study drug must not be used for reasons other than that described in the protocol.	Clarification on patient compliance of IP administration
Section 9.5 Randomization	An IWRS will be utilized to randomize patients 1:1 to bardoxolone methyl or placebo. Randomization will be stratified by eligibility eGFR category (30 to <60; ≥60 to 90), concomitant tolvaptan use (yes, no), and screening ACR (≤300 mg/g, >300 mg/g). Eligibility eGFR is the average of Screening eGFR visits. Randomization should occur on Day 1, as a Day 1 study procedure. Where this is not possible, due to logistical issues at the level, and randomization occurs prior to Day 1, this will result in a protocol deviation. When randomization occurs prior to Day 1, the site must confirm eligibility prior to randomizing the patient in the IWRS. ~~The patient visit schedule is based on date of randomization.~~	Clarification on randomizing patients

Section	Version 5	Rationale
Section 9.6.3 Data Monitoring Committee	An independent DMC will review unblinded safety data throughout the study and make recommendations as appropriate. The DMC will begin data reviews approximately 3 months after the first patient is enrolled and continue ~~quarterly~~regular reviews through the last dose of the last patient enrolled. The DMC will consist of external experts supported by an independent statistical group which will prepare unblinded analyses for the DMC and will have no role in the statistical analysis plan (SAP) after the study has started enrolling patients. A separate statistical group not associated with the DMC will be responsible for producing and finalizing the SAP and executing final data analysis of the study~~, including the Week 52 analysis for the primary endpoint.~~	Updated to reflect change in endpoints to add flexibility for cadence.
Section 9.7 Unscheduled Visits	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 and ~~IP~~dosing diary. Additional conversations may be necessary with the medical monitor following an unscheduled visit to assess patient safety.	Removed undefined abbreviation and replaced with "dosing"

Section	Version 5	Rationale
Section 9.8.2 Methods of Birth Control	During Screening, while taking study drug and until 30 days following administration of the final dose of study medication, WOCBP must practice one of the following acceptable methods of birth control: • Use double barrier contraception method defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream, diaphragm (always use with spermicidal jelly/cream)); • Use of hormonal contraceptives (oral, parenteral, intravaginal, or transdermal) for at least 9060 days prior to start of study drug administration; • Use of an intrauterine device; • Vasectomized partner (with vasectomy performed at least 6 months prior to screening with the appropriate post-procedure documentation of surgical success). Partner must be the sole partner for that patient; • Abstain from sexual intercourse completely. Complete abstinence from heterosexual intercourse is only acceptable if it is the preferred and usual lifestyle of the individual. Periodic abstinence is not permitted.	Update for use of hormonal contraceptives use to align with updated screening window
Section 9.10 Study Procedures	Every effort should be made to ensure all assessments are conducted at in-person visits. In certain cases and with prior sponsor approval, if a patient is unable or unwilling to come to the clinic for in-person assessments, the conduct of study procedures by home health nurses is permissible and should be considered as an alternative to a missed or skipped visit.	Updated to add clarification on in-person visits and the potential to use home health visits to conduct study procedures in cases where a patient is unwilling or unable to come to the site

Section	Version 5	Rationale
Section 9.10.7 Weight and Body Mass Index (BMI)	Weight must be measured as indicated in Table 4. BMI will be calculated in the eCRF each time the weight is recorded. The Sponsor will provide 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~~study, 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 per the criteria~~during the first eight 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.	Updated to reflect change in weight recording criteria
Section 9.10.11 Physical Examination & Targeted Examination	A targeted physical examination (symptom-directed) should be performed as needed at visits indicated in Table 4.	Addition of targeted examinations to protocol procedures
Section 9.10.13 Study Drug Administration	For dose levels up to 20mg, p~~P~~atients should self-administer one capsule ~~from each bottle included in the study drug kit~~ orally once a day beginning at Day 1 through the end of the study, as indicated in Table 4. Patients who dose escalate to 30 mg should administer two capsules orally once a day. Each dose of study drug should be administered at approximately the same time each day, ~~preferably in the morning.~~ Study drug administration (IP) should be recorded in a patient diary through Week 100. On days when PK samples are collected, patient must not self-administer study drug. Study staff will administer study drug at the clinic following collection of the first PK sample.	Clarification on IP dosing and preference for morning intake as food effect studies do not support the need or a morning dosing.

Section	Version 5	Rationale
Section 9.10.16 Adverse Event Collection	Patients will be observed for general appearance, presence of illness or injury, or signs indicative of a concurrent illness as indicated in Table 4. Patients must be instructed to volunteer any information regarding AEs on or after the first dose of study drug or sites may 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. AEs should be reported from the time of the first dose through 30 days after the last dose (or the End of Study visit, whichever is earlier).	Clarification on Adverse Event Collection
Section 9.10.17 Kidney Ultrasound	Kidney ultrasound (historical or an ultrasound performed at Screen A) may be used ~~at Screen A~~ to diagnose ADPKD and to assess for eligibility based on the Modified Pei-Ravine Criteria. Patients with prior diagnosis of ADPKD will not have a kidney ultrasound performed as part of the study~~,~~ but must provide documentation of ADPKD diagnosis for eligibility.	Updated language
Section 9.10.22 Coagulation	Samples will be collected for the following coagulation assessments as indicated in Table 4: Prothrombin Time (PT), and International Normalized Ratio (INR).	PT and INR added to obtain complete liver function assessment

Section	Version 5	Rationale
Section 9.10.23 Lipid Panel	Samples will be collected for the following lipid assessments as indicated in Table 4: Total Cholesterol, Low-Density Lipoprotein (LDL), High-Density Lipoprotein (HDL), and Triglycerides.	Lipid Panel added to understand the baseline clinical condition in the population, as hyperlipidemia is common in CKD
Section 9.10.24 SARS-CoV-2 Antibody Testing	Samples will be collected for SARS-CoV-2 antibody testing as indicated in Table 4.	Added SARS-CoV-2 antibody testing to determine whether patients contract SARS-CoV-2 and remain asymptomatic, as SARS-CoV-2 infection can impact kidney function
Section 9.10.31 Pharmacokinetic (PK) Blood Samples	Patients who have discontinued study drug should not complete PK procedures.	Clarification

Section	Version 5	Rationale
Section 11.2.1.1 Adverse Event	All AEs that are observed or reported by the patient during the study (from the time of administration of the first dose at the Day 1 visit until the final visit indicated in Table 4) must be reported, regardless of their relationship to study drug or their significance. For patients who discontinue study drug early, AEs should be reported through 30 days following the date of last dose of study drug.	Clarification
Section 11.2.1.2 Serious Adverse Event	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 the first dose of study drug until the final visit indicated in Table 4, as appropriate), including events resulting from protocol-associated procedures as defined in relevant legislation, and regardless of their relationship to study drug or their clinical significance. For patients who discontinue study drug early, SAEs should be reported through 30 days following the date of last dose of study drug, with the exception of death, kidney transplant, or initiation of dialysis, which should be reported through Week 104 (See Section 11.7).The sponsor may request additional information from the investigator to ensure the timely completion of accurate safety reports.	Clarification
Section 11.4 Assessment of Causality	For regulatory reporting purposes, an adverse event is considered to be related when the causality evaluation is either "Definitely Related, Probably Related, or Possibly Related." An adverse even is considered to be not related when the causality evaluation is either "Unlikely Related or Not Related."	Clarification
Section 11.6 Recording Adverse Events	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, or stabilization). All other AEs will be followed through the final visit indicated in Table 4, as appropriate.	Clarification

Section	Version 5	Rationale
Section 12.1 Sample Size	With ~~300~~550 patients enrolled, the study will have approximately 80% power to detect a difference between the two treatment groups in change from baseline eGFR of 3.1 mL/min/1.73 m^2. The power calculation was based on a 2-sample t-test as an estimate for the planned ANCOVA analysis and assume the following: • Overall two-sided Type I error rate total of 0.05; 0.025 allocated to primary endpoint and 0.025 allocated to the key secondary endpoint; • Proportion of patients with missing off-treatment data not exceed 15%; • Standard deviation of change from baseline in eGFR of 812 mL/min/1.73 m2; • Analyses are based on the intent-to-treat (ITT) population; • Missing data are not imputed (sensitive analyses, including a tipping point analysis, will be performed to assess the impact of the missing data).	Updated information
Section 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 site personnel and the responsible monitor during monitoring visits, and those observations will be communicated to the investigator. Protocol deviations will be reviewed and any that are a serious breach of GCP and/or the protocol will be reported to the relevant regulatory agency, as required. Protocol waivers are not allowed for sites in the United Kingdom, and protocol waivers will not be granted by the Sponsor in any participating countries. 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.	Clarification

Section	Version 5	Rationale
Section 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, or for the duration required by local regulations, whichever is longer. 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.	Clarification

AMENDMENT CHANGE DOCUMENT
CLINICAL STUDY PROTOCOL 402-C-1808
Study Title: A Phase 3 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with Autosomal Dominant Polycystic Kidney Disease

Protocol History

Version 01	12 December 2018
Version 02	4 March 2019
Version 03	16 July 2019
Version 04	25 June 2020

Confidentiality Statement

SUMMARY OF CHANGES

The following document outlines the changes that have been made to Version 3 to produce the text of Version 4. Additionally, the following points are provided:

- New text that is added is marked with an underscore; text that has been deleted is marked with a ~~strikethrough~~.
- The changes made in the body of the protocol are reflected in the synopsis; the corresponding changes made in the synopsis are not described.
- Grammatical corrections and minor editorial changes are not described.
- Section numbers refer to the numbers in the new version of the protocol.

Section	Version 4	Rationale
Emergency Contact Information	[redacted] E-mail: [redacted] [redacted] ~~E-mail:~~ [redacted]	Updated contact information for SAE Reporting
Section 2 Synopsis	**Study center(s):** Up to 150~~100~~ study centers	Increased number of study centers due to increased sample size.
Section 4 List of Abbreviations and Definitions of Terms	COVID-19 Coronavirus Disease 2019 ~~CRO Clinical Research Organization~~ ICH International ~~Conference on Harmonization~~ Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ~~J2R~~ Jump ~~to reference~~ ~~MMRM~~ Mixed ~~model repeated measures~~ ~~NF-κB~~ Nuclear ~~factor kappa light chain enhancer of activated B cells~~ SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2 UACR Urine albumin to creatinine ratio	Updated list of abbreviations.

<table>
<tr><th>Section</th><th>Version 4</th><th>Rationale</th></tr>
<tr><td>Section 5.1
Clinical Experience with Bardoxolone Methyl</td><td>Overall, bardoxolone methyl has been tested in multiple~~eight~~ CKD studies enrolling over 3,000~~2,700~~ patients and over 3,000~~2,000~~ individuals have been exposed to bardoxolone methyl.</td><td>Updated information</td></tr>
<tr><td>Section 5.1.1
Efficacy</td><td>Notably, Reata's Asian development partner, Kyowa ~~Hakko~~ Kirin Co., Ltd, demonstrated that bardoxolone methyl treatment resulted in a significant improvement in measured GFR, as assessed by inulin clearance, in Japanese patients with CKD and type 2 diabetes.</td><td>Updated information</td></tr>
<tr><td>Section 5.1.1
Efficacy (Table 3)</td><td>
<table>
<tr><td>RTA402-005 (TSUBAKI)</td><td>2/ Japan</td><td>Age ≥ 20, T2D and Stage 3 and 4 CKD</td><td>~~108~~ 120</td><td>16 weeks</td><td>6.6 (inulin GFR) (p=0.008 vs PBO)</td></tr>
<tr><td>402-C-1603</td><td>2/US</td><td>Age 12 to 65, Alport Syndrome</td><td>30</td><td>~~12~~ 48 weeks</td><td>~~13.4 (p<0.001)~~ 10.4 (p<0.0001)</td></tr>
<tr><td>402-C-1603 (Year 1)</td><td>3/Global</td><td>Age 12 to 70, Alport Syndrome</td><td>157</td><td>48 weeks</td><td>9.5 (p<0.001 vs PBO)</td></tr>
<tr><td>402-C-1702</td><td>2/US</td><td>Age 18 to 70, ADPKD</td><td>31</td><td>12 weeks</td><td>9.3 (p<0.0001)</td></tr>
<tr><td>402-C-1702</td><td>2/US</td><td>Age 18 to 70, IgA Nephropathy</td><td>26</td><td>12 weeks</td><td>8.0 (p<0.0001)</td></tr>
<tr><td>402-C-1702</td><td>2/US</td><td>Age 18 to 70, T1D CKD</td><td>28</td><td>12 weeks</td><td>5.5 (p=0.025)</td></tr>
<tr><td>402-C-1702</td><td>2/US</td><td>FSGS</td><td>18</td><td>12 weeks</td><td>7.8 (p=0.003)</td></tr>
</table>
</td><td>Updated data for the Cross-Study Comparison of Increases in eGFR, Inulin Clearance, and Creatinine Clearance with Bardoxolone Methyl Treatment</td></tr>
<tr><td>Section 6.1 1
Primary Objective</td><td>• To assess the off-treatment change from baseline in estimated glomerular filtration rate (eGFR) at Week 52 or following a 4-week drug treatment withdrawal period in the first year of treatment.</td><td>Clarification</td></tr>
</table>

Section	Version 4	Rationale
Section 6.1 2 Key Secondary Objective	• To assess the off-treatment change from baseline in eGFR at Week 104 or following a 4-week drug treatment withdrawal period in the second year of treatment.	Clarification
[redacted]	[redacted]	[redacted]

Section	Version 4	Rationale
[redacted]	[redacted]	[redacted]
Section 6.2.1 Primary Efficacy Endpoint	• Off-treatment change~~Change~~ from baseline in eGFR at Week 52 (or following a 4-week drug treatment withdrawal period in the first year of treatment).	Clarification
Section 6.2.2 Key Secondary Efficacy Endpoint	• Off-treatment change~~Change~~ from baseline in eGFR at Week 104 (or following a 4-week drug treatment withdrawal period in the second year of treatment).	Clarification

Section	Version 4	Rationale
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Section	Version 4	Rationale
Section 7.1 Overall Study Design	Randomization will be stratified by eligibility ~~baseline~~ eGFR category (30 to ≤60; ≥60 to 90), concomitant tolvaptan use (yes, no), and screening ACR (≤300 mg/g, >300 mg/g).	Clarification that patients with an eligibility eGFR of 60 should be stratified to the ≥60 to 90 category, and clarification made to include all stratification factors (no IRT changes made).
Section 7.1 Overall Study Design	The conduct of the study, according to protocol specifications, was impacted by the COVID-19 (Coronavirus Disease 2019) pandemic. As a result, and as of Version 4 of the Protocol, modifications intended to address access to and administration of investigational product (IP), and adherence to protocol-specified visits and laboratory assessments were implemented. These modifications are described in Appendix 1 (COVID-19 Mitigations).	COVID-19 Mitigation Appendix (Appendix 1) added to describe protocol modifications due to the COVID-19 pandemic.
Section 7.3.1 Dose Escalation	Dose escalation may need to proceed more slowly if the patient experiences early elevations in ALT/AST over ULN, e.g. at Week 2 (see Section 9.1.2). The dosing objective is to titrate patients to the maximum 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, or 6 with the medical monitor.	Added guidance for managing ALT and AST elevations > ULN during the dose titration period.
Section 7.5 Schedule of Assessments (Table 4)	Assessment Wk 104 (A) or Follow-up (A)[l,m] Assessment Wk 104 (B) or Follow-up (B)[l,m]	Clarification

Section	Version 4	Rationale
Section 7.5 Schedule of Assessments (Table 4)	[j] Patients must be instructed to not take their study drug prior to coming to the clinic for visits when PK samples will be collected. Patients must administer the study drug dose in the clinic on PK sample collection visits after the 0 hour PK blood sample is collected. Patients will have blood samples for PK analysis drawn just prior to (0 hour) and after (2 and 4 hours) dose administration. If PK sampling is unable to be performed during the Week 12 visit, samples may be collected at Week 24, 36 or 48.	Additional options for PK sampling are available, if sampling is unable to be performed at Week 12.
Section 7.5 Schedule of Assessments (Table 4)	[k] Both Week 52 visits must be completed 21 to 35 days after last dose in year 1, and before re-dispensing study drug. [l] Patients who terminate from the study prior to the Week 100 study visit should be brought back to the clinic as soon as possible for early termination assessments (i.e., end-of- treatment visit) as well as two ~~a~~ follow-up ~~visit 4 weeks later~~ visits within 21 to 35 days after the last dose. [m] Both Week 104 visits must be completed 21 to 35 days after last dose in year 2.	Clarification of when the off-treatment visits should occur.
Section 7.5 Schedule of Assessments (Table 4)	Abbreviations: ACR = albumin to creatinine ratio, ADPKD = autosomal dominant polycystic kidney disease, AE = adverse event, BNP = B-type natriuretic peptide, [redacted], EC = ethics committee, ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, IP = investigational product, IRB = institutional review board, NT-proBNP = N-terminal pro-brain natriuretic peptide, [redacted], PK = pharmacokinetic, Wk = week, WOCB = women of child-bearing potential	Clarification made to define abbreviations used in Table 4.
Section 8.1 Patient Inclusion Criteria	5. Systolic blood pressure ≤ 140 mmHg and diastolic blood pressure ≤ 90~~80~~ mmHg at Screen A visit after a period of rest.	Inclusion of patients with diastolic blood pressure ≤ 90 mmHg is permitted.

Section	Version 4	Rationale
Section 8.2 Patient Exclusion Criteria	2. Concomitant use of tolvaptan is excluded. Patients previously treated with tolvaptan must have discontinued drug for at least 3 months prior to Screen A visit ~~and had no history of elevations of ALT or AST > ULN while they were receiving tolvaptan~~. Initiation of concomitant tolvaptan use during the study is not permitted;	Patients previously treated with tolvaptan with a history of elevations of ALT or AST > ULN while receiving tolvaptan are not excluded from the study.
Section 8.4 Patient Re-Screening	Patients may repeat the Screening procedures once to qualify for the study (re-screening must occur at least 2 weeks after the screen fail) ~~with approval from the medical monitor~~. In rare circumstances, a second re-screen may be appropriate; in these cases the site must consult with the medical monitor for approval. If a patient is approved to re-screen, they are given a new patient number and all screening procedures are completed.	Clarifications to the process of re-screening.

Section	Version 4	Rationale
Section 8.5.1 Patient Study Drug Discontinuation Criteria	For patients who permanently discontinue study drug and are no longer willing to return for all scheduled study visits, a number of follow-up options are available and must be discussed with the patient thoroughly, including: • Participation in follow-up procedures specified in the protocol by an in-home visit, where feasible; • Reduced in-person visit schedule; • Telephone contact only; • Contact of alternative person(s) who has been designated in source records as being available to discuss the patient's medical condition; • Non-direct follow-up of patient information including obtaining additional information from the patient's medical records (e.g., ESKD or death). These reduced follow-up options should be discussed with any patient considering study termination following permanent discontinuation of drug. The frequency and schedule of participation in follow-up procedures, whether in-clinic, by telephone, by in-home visit(s) or some other means, should be discussed and agreed to by patient and staff. All efforts to prevent the patient from progressing to a "Lost to Follow-Up" status must be made at the time of permanent study drug discontinuation. Any discussions about reduced follow-up options must be documented in the patient's source file and discussed with the study manager.	Added additional reduced follow-up options for patients who permanently discontinue study drug and clarified how these options should be discussed and documented.

Section	Version 4	Rationale
Section 8.5.1 Patient Study Drug Discontinuation Criteria	A patient who permanently discontinues treatment anytime prior to Week 100 will have an end of treatment visit as close as possible to the day of last dose. The patient will then complete both Follow-up A and Follow-up B visits within 21 to 35 days after last dose. Safety and clinical chemistry assessments, including a serum creatinine assessment for efficacy, will be performed at the end of treatment and follow-up visits. After the follow-up visits, the patient will continue with all assessments up to and including their scheduled Week 52 and Week 104 visits.	Clarification of the timing of the end of treatment visit, follow-up visits, and subsequent study visits for patients who discontinue treatment prior to Week 100. Clarification of the assessments performed at the follow-up visits.
Section 8.5.2 Patient Study Termination Criteria	Follow-up options described in Section 8.5.1 should be discussed, as soon as possible, with patients who no longer wish to return for all scheduled in-person visits, patients who have failed to return for a scheduled visit, and patients who may be demonstrating an increasing risk of no longer communicating with the site. Patients should not be considered lost to follow-up until the scheduled Week 104 visit date.	Clarifying language about when follow-up options in Section 8.5.1 should be discussed and with which patients they should be discussed.

Section	Version 4	Rationale
Section 8.5.2 Patient Study Termination Criteria	The term "withdrawal of consent" should be used only when the patient no longer wishes to participate in the trial and no longer authorizes investigators to make efforts to continue to obtain their outcome data. Unless the patient provides their written withdrawal of consent or there is other written documentation by the investigator confirming the patient's verbal intent to completely withdraw from the trial, patients should be followed for all protocol specified evaluations and assessments. The investigator should inquire about the reason for withdrawal of consent, request the patient return all unused investigational product, request the patient return for end-of-treatment and follow-up visits (if applicable), and follow-up with the patient regarding any unresolved AEs. Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a patient's intended withdrawal need to be completely understood, documented and managed to protect the rights of the patient and the integrity of the trial. Only patients who withdraw their permission for all of the follow-up options outlined in Section 8.5.1 are considered to have completely withdrawn their consent to participate in the study.	Clarification of withdrawal of consent.
Section 9.1.1 Management of Fluid Status	Beyond Week 8, patients~~Patients~~ who experience a weight increase of five-pounds (2.3 kilograms) or greater compared to Day 1~~increase in weight after the Week 8 study visit~~ will be instructed to contact the clinic to assess the need for an unscheduled physical examination and laboratory assessment by the investigator.	Clarification

Section	Version 4	Rationale
Section 9.1.2 Management of Elevated Transaminase Levels (ALT and/or AST)	For only patients who enrolled under Version 2 of the protocol and ~~who~~ are receiving tolvaptan (JYNARQUE), liver biochemistries (ALT, AST, and/or bilirubin levels) should be monitored according to the relevant package insert/REMS program for tolvaptan. For all patients enrolled, nearly~~Nearly~~ all instances of elevated transaminases due to bardoxolone methyl treatment are expected to be asymptomatic. Some patients may experience more rapid increases in ALT/AST values than others during the dose titration period. Investigators may consider extending the time between each dose increase from two weeks to four weeks to manage ALT/AST elevations.~~If ALT or AST levels reach approximately 2X ULN or more during dose escalation, the investigator should discuss with the medical monitor consideration of slowing titration or down titrating.~~	Added guidance for managing ALT and AST elevations during the dose titration period.
Section 9.1.2 Management of Elevated Transaminase Levels (ALT and/or AST)	Repeat testing every 72 to 96 hours until transaminase levels are below 3X the ULN for at least one week. Testing for patients not located near the investigator (such that it is not practical to return to the site at the required intervals) may be performed by a home health nurse using a central lab kit, or at a local lab and sent to the investigator and medical monitor for review, by approval from the medical monitor.	Added an option to allow repeat testing of transaminase levels to be conducted by a home health nurse with a central lab kit for patients with ALT or AST elevations > 3X ULN who are not located near the investigator.

Section	Version 4	Rationale
Section 9.1.2 Management of Elevated Transaminase Levels (ALT and/or AST)	Discontinue study drug administration temporarily and contact the medical monitor to discuss if ~~permanent study drug discontinuation is required 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 study drug may be restarted with the Sponsor's approval after the following criteria are fulfilled: • Ultrasound of the hepatobiliary tree; • ALT and AST returned to < ULN; • TBL is within normal range; • Other relevant labs (e.g., albumin, INR, PT) are within normal range; • No clinical signs or symptoms of liver injury are present. Patients restarting study drug should start at the 5 mg dose level and dose titrate according to Section 7.3.2.	Added procedures for restarting study drug after a temporary discontinuation due to elevated ALT or AST.
Section 9.1.3 Management of Muscle Spasms	Serum vitamin D levels may be collected by the investigator, in the evaluation of muscle spasms. If vitamin D levels are low, supplementation may be warranted.	Clarification
Section 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 urine albumin to creatinine ratio (UACR) < 30 mg/g, and ≤ 130 mm Hg systolic and ≤ 80 mmHg diastolic for patients with UACR > 30 mg/g (KDIGO, 2012).	Clarification

Section	Version 4	Rationale
Section 9.1.9 End Stage Kidney Disease	Two off-treatment serum creatinine assessments should be collected 21 to 35 days after last dose, and prior to initiation of dialysis or receipt of transplant.	Clarification
Section 9.2 Description of Study Drug (Table 5)	Description Bardoxolone methyl capsule (5 mg, 10 mg, 15 mg, 20 mg~~, 30 mg~~)	The 30 mg strength bardoxolone methyl capsules and size matched placebo capsules will not be used.
Section 9.2 Description of Study Drug (Table 6)	Description[a] Placebo for bardoxolone methyl capsule (size #4, size #2, size #1, and size #0~~, and size #00~~)	The 30 mg strength bardoxolone methyl capsules and size matched placebo capsules will not be used.
Section 9.5 Randomization	Randomization will be stratified by ~~baseline~~ eligibility eGFR category (30 to ≤60; ≥60 to 90), concomitant tolvaptan use (yes, no), and screening ACR (≤300 mg/g, >300 mg/g). Eligibility eGFR is the average of Screening eGFR visits.	Clarification that patients with an eligibility eGFR of 60 should be stratified to the ≥60 to 90 category, and clarification made to include all stratification factors (no IRT changes made).

Section	Version 4	Rationale
Section 9.8 Pregnancy	**9.8.1 Women of Childbearing Potential and Fertile Males** Women of childbearing potential (WOCBP) are those who have experienced menarche and are not surgically sterile (no history of bilateral tubal ligation, hysterectomy, bilateral salpingectomy, or bilateral ~~salpingo-~~oophorectomy), do not have fallopian inserts with confirmed blockage (e.g., x-ray, ultrasound), have not had reproductive potential terminated by radiation, and are not postmenopausal (defined as no menses for at least 1 year without an alternative medical cause). Fertile males are those who have entered puberty or reached physical maturation (after puberty), and are not surgically sterile (no history of bilateral orchiectomy or vasectomy at least 6 months earlier with the appropriate post-procedure documentation of surgical success).	Clarifications to the definition of WOCBP. Definition of fertile males added for clarity.

Section	Version 4	Rationale
Section 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]). ~~Double barrier method is not allowed for patients at participating sites in Germany~~; • Use of hormonal contraceptives (oral, parenteral, intravaginal, or transdermal) for at least 90 days prior to start of study drug administration; • Use of an intrauterine device; • Vasectomized partner (with vasectomy performed at least 6 months prior to screening with the appropriate post-procedure documentation of surgical success). Partner *must* be the sole partner for that patient; • Abstain from sexual intercourse completely. Complete abstinence from heterosexual intercourse is only acceptable if it is the preferred and usual lifestyle of the individual. Periodic abstinence is not permitted.	Clarifications to acceptable methods of birth control for WOCBP. Double barrier method is not allowed for participating sites in Germany which is stated in the country-specific protocol only.

Section	Version 4	Rationale
Section 9.8.2 Methods of Birth Control	During Screening, while taking study drug and until 30 days after the final dose of study medication is taken, fertile males who have female partners of childbearing potential must practice one of the following methods of birth control: ~~• 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])~~. Double barrier method is not allowed for patients at participating sites in Germany~~; • Partner contraception methods; *must* be the sole partner for that patient: – ~~Partner use~~Use of an intrauterine device; – ~~Partner use~~Use of hormonal contraceptives (oral, parenteral, intravaginal or transdermal) for at least 90 days prior to start of study drug administration; – Surgically sterile partner (bilateral tubal ligation, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy); fallopian inserts with confirmed blockage (e.g. x-ray, ultrasound); – Reproductive potential has been terminated by radiation; – Postmenopausal (defined as no menses for at least 1 year) without an alternative medical cause. • Abstain from sexual intercourse completely. Complete abstinence from heterosexual intercourse is only acceptable if it is the preferred and usual lifestyle of the individual. Periodic abstinence is not permitted.	Clarifications to acceptable methods of birth control for fertile males. Double barrier method is not allowed for participating sites in Germany which is stated in the country-specific protocol only.

Section	Version 4	Rationale
Section 9.10.4 Prior and Current Concomitant Medications	Prior and concomitant~~Concomitant~~ medications (i.e., medications that the patient is taking or has taken within 30 days prior to Day 1) will be reviewed as indicated in Table 4 and all changes will be recorded.	Clarification
Section 9.10.13 Study Drug Administration	Study drug administration (IP) should be recorded in a patient diary ~~at least~~ through Week 100~~12~~.	Clarification
Section 10.1 Study Drug	Bardoxolone methyl capsules, 5 mg (size #4), 10 mg (size #2), 15 mg (size #1), and 20 mg (size #0)~~, and 30 mg (size #00)~~ may be used in this study. The 30 mg dose will be given as ~~either~~ two 15 mg capsules~~ or one 30 mg capsule~~.	The 30 mg strength bardoxolone methyl capsules and size matched placebo capsules will not be used.
Section 10.2 Study Drug Packaging and Labeling	The study drug will be supplied as either individual bottles (5, 10, 20~~, and 30~~ mg dose) or in tamper-evident kits containing two high-density polyethylene (HDPE) bottles (30 mg dose as 2 x 15 mg capsules). 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, 10 mg, 15 mg, or 20 mg~~, or 30 mg~~ strength bardoxolone methyl or the matching placebo capsules.	The 30 mg strength bardoxolone methyl capsules and size matched placebo capsules will not be used.

Section	Version 4	Rationale
Section 11.7 Reporting Serious Adverse Events	To report the SAE, fax or email the completed SAE form [redacted] within 24 hours of awareness. [redacted] [redacted] E-mail: [redacted] [redacted] ~~E-mail:~~ [redacted] **For questions regarding SAE reporting, contact your study manager, medical monitor,** [redacted] **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 [redacted]	Updated contact information for SAE Reporting.

Section 12.1 Sample Size	With 300 patients enrolled, the study will have approximately 80% power to detect a difference between the two treatment groups in change from baseline ~~in~~ eGFR of 3.1~~2.2~~ mL/min/1.73 m^2 ~~at Week 48~~. The power calculation~~, which~~ was based on ~~mixed model repeated measures (MMRM)~~a 2-sample t-test as an estimate for the planned ANCOVA analysis~~,~~ and assumes the following: ~~• 9 repeated measurements (Weeks 1, 2, 4, 6, 8, 12, 24, 36, and 48);~~ ~~• The correlation between observations on the same subject is 0.7;~~ ~~• Two-sided Type I error rate of 0.05;~~ • ~~Standard deviation of change from baseline in eGFR of 8 mL/min/1.73 m^2;~~ ~~• Analyses are based on the intent-to-treat (ITT) population;~~ ~~• No imputation for missing data since all patients are included in MMRM analysis.~~ ~~The analysis of efficacy will use an unstructured covariance structure, which is expected to have approximately the same power as the analysis with compound symmetry used for study planning.~~ ~~Analysis of covariance (ANCOVA) will be used for analysis of the off-treatment endpoints (i.e., Week 52 and Week 104). Using a two-sample t-test to estimate power for the ANCOVA analysis, the study will have approximately 80% power to detect a difference between the two treatment groups in change from baseline in eGFR of 2.6 mL/min/1.73 m^2. The power calculation assumes the following:~~ • Overall two-sided Type I error rate total of 0.05; 0.025 allocated to primary endpoint and 0.025 allocated to the key secondary endpoint; • ~~Two-sided Type I error rate of 0.05;~~ • Proportion of patients with missing off-treatment data not to exceed 15%; • Standard deviation of change from baseline in eGFR of 8 mL/min/1.73 m^2; • Analyses are based on the intent-to-treat (ITT) population; • Missing data are not imputed (sensitivity analyses, including a tipping point analysis, will be performed to assess the impact of missing data).~~using multiple imputation;~~	Removed the power calculation for on-treatment endpoints. The study has approximately 80% power to detect an off-treatment difference between the treatment groups of 3.1, which allows for up to 15% of patients with missing off-treatment data. The power calculation assumes that the overall two-sided Type I error rate is split between the primary and key secondary endpoint and that missing data is not imputed.

Section	Version 4	Rationale
	ANCOVA analysis is expected to have approximately the same power as the t-test used for study planning. The method for maintaining strict control of the Type I error for the trial will be described in the statistical analysis plan (SAP). Appropriate sensitivity analyses of the primary analysis will be specified in the SAP.	
Section 12.3 Statistical Analyses	Data will be summarized ~~overall~~ using descriptive statistics.	Clarification
Section 12.3 Statistical Analysis	**12.3.1 ~~Primary~~ Analysis of Efficacy** The ITT population, which includes all patients randomized within each cohort, will be used as the population for assessment of the ~~primary~~ efficacy endpoints. ~~Mixed-model repeated measures (MMRM) analyses will be used to analyze the on-treatment efficacy endpoints of change from baseline in eGFR at Week 48 and Week 100. 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 as a continuous covariate. Other covariates may be specified in the SAP. Time ordering is a repeated measure within patients. It is assumed that errors for different patients are independent with an unstructured covariance structure. Missing data will not be imputed for the primary analysis since all data collected will be included in the MMRM analysis. Appropriate sensitivity analyses will be performed and defined in the SAP.~~ Analysis of covariance (ANCOVA) will be used to analyze the ~~off-treatment~~ primary and key secondary efficacy endpoints of change from baseline in off-treatment eGFR ~~at Week 52 and Week 104. The dependent variable will be change from baseline in eGFR.~~ The model will include change from baseline in eGFR as the dependent variable, treatment group as fixed effect, and baseline eGFR as a continuous covariate. Other covariates may be specified in the SAP. The off-treatment endpoints assess the preserved drug benefit relative to placebo following withdrawal of treatment; therefore, analyses of these endpoints do not include eGFR values collected during treatment. Missing data are not imputed ~~for ANCOVA analyses using multiple imputation~~. Sensitivity analyses, including a tipping point analysis, will be performed to assess the impact of missing data.	Details of the MMRM analyses for the on-treatment efficacy endpoints will be specified in the Statistical Analysis Plan. Clarified and added language describing the planned analyses of the primary and key secondary efficacy endpoints, including how missing data will be handled.

Section	Version 4	Rationale
Section 13.1 Study Monitoring	The Sponsor or designee will monitor all aspects of the study for compliance with applicable government regulation with respect to the International ~~Conference on~~Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline E6(R2): Good Clinical Practice: Consolidated Guideline and current standard operating procedures.	Updated to full definition of ICH.
Section 14.4 Investigator Documentation	• A Form FDA 1572 or equivalent statement of investigator, fully executed, and all updates on a new fully executed Form FDA 1572;	Clarification
Section 15.2 Ethical Conduct of the Study	The principal investigator agrees to conduct the study in accordance with the International ~~Conference on Harmonization~~Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) for Guidance for Industry on Good Clinical Practice (GCP) ICH E6(R2) [https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf] and the principles of the Declaration of Helsinki [https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/].	Updated to full definition of ICH.
Appendix 1 COVID-19 Mitigations	Appendix 1 (COVID-19 Mitigations) was added.	COVID-19 Mitigation Appendix (Appendix 1) added to describe protocol modifications due to the COVID-19 pandemic.

AMENDMENT CHANGE DOCUMENT
CLINICAL STUDY PROTOCOL 402-C-1808
Study Title: A Phase 3 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with Autosomal Dominant Polycystic Kidney Disease

Protocol History

Version 01	12 December 2018
Version 02	4 March 2019
Version 03	16 July 2019

Confidentiality Statement

SUMMARY OF CHANGES

The following document outlines the changes that have been made to Version 2 to produce the text of Version 3. Additionally, the following points are provided:

- New text that is added is marked with an underscore; text that has been deleted is marked with a ~~strikethrough~~.
- The changes made in the body of the protocol are reflected in the synopsis; the corresponding changes made in the synopsis are not described.
- Grammatical corrections and minor editorial changes are not described.
- Section numbers refer to the numbers in the new version of the protocol.

Section	Version 3	Rationale
Emergency Contact Information	[redacted] [redacted] Office: [redacted] ~~Mobile:~~ [redacted] -Email: [redacted]	Updated personnel
Section 4 List of Abbrevations and Definitions of Terms	ADPKD Autosomal Dominant Polycystic Kidney Disease [redacted]	Updated terms
Section 6.2.3 Secondary Efficacy Endpoints	Change from baseline in eGFR ~~after~~ at Week 48 ~~weeks of treatment~~. Change from baseline in eGFR ~~after~~ at Week 100 ~~weeks of treatment~~.	Clarification
Section 7.1 Overall Study Design	Patients will be randomized 1:1 to either bardoxolone methyl or placebo. Randomization will be stratified by baseline eGFR category (30 to 60; 60 to 90) ~~and concomitant tolvaptan use at baseline (yes; no).~~	Patients receiving concomitant Tolvaptan are excluded from study
[redacted]	[redacted]	Clarification

Section	Version 3	Rationale
Section 8.1 Patient Inclusion Criteria	~~10. Concomitant use of tolvaptan during the study is permitted if the following criteria are met:~~ ~~a. Patient must have been receiving tolvaptan for at least 6 months prior to Screen A visit;~~ ~~b. Patient must be receiving stable dose of tolvaptan for at least 8 weeks prior to Screen A visit;~~ ~~c. ALT and AST must be within normal limits (≤ ULN) at Screen A visit;~~ ~~d. Patient has no history of elevations of ALT or AST > ULN while receiving tolvaptan;~~ ~~e. Tolvaptan dose is not expected to change or be stopped during the trial.~~	Patients receiving concomitant Tolvaptan are excluded from study
Section 8.2 Patient Exclusion Criteria	2. Concomitant use of tolvaptan is excluded. Patients previously treated with tolvaptan must have discontinued drug for at least 3 months prior to Screen A visit and had no history of elevations of ALT or AST > ULN while they were receiving tolvaptan. Initiation of concomitant tolvaptan use during the study is not permitted;	Patients receiving concomitant Tolvaptan are excluded from study
Section 9.1.2 Management of Elevated Transaminase Levels (ALT and/or AST)	For patients enrolled under Version 2 of the protocol and who are receiving tolvaptan (JYNARQUE), liver biochemistries (ALT, AST, and/or bilirubin levels) should be monitored according to the relevant package insert/REMS program for tolvaptan.	Clarification
Section 9.3.1 Excluded Medications	Patients taking these medications or treatments will be ineligible for enrollment: • Tolvaptan (patients on tolvaptan who have already enrolled in FALCON under Version 2 of the protocol may remain in the trial); • Somatostatin analogues	Medications which could confound safety/efficacy evaluation, including Tolvaptan, are excluded

Section	Version 3	Rationale
Section 9.3.1 Excluded Medications	Concomitant use with strong CYP3A4 inhibitors is prohibited. If a strong CYP3A4 inhibitor is medically necessary, study drug should be temporarily discontinued. Concomitant study drug use with moderate CYP3A4 inhibitors should be avoided whenever possible, and switching to an alternative agent should be considered. When concomitant use of a moderate CYP3A4 inhibitor is unavoidable, patients should be carefully monitored and the study drug dose may be temporarily reduced or temporarily discontinued at the discretion of the investigator. Concomitant use with strong CYP3A4 inducers is prohibited. ~~Concomitant study drug use with CYP3A4 inhibitors should be avoided whenever possible, and switching to an alternative agent should be considered for CYP3A4 inhibitors. When concomitant use of a CYP3A4 inhibitor is unavoidable, patients should be carefully monitored. If a strong CYP3A4 inhibitor is medically necessary, the study drug dose may be temporarily reduced or temporarily discontinued at the discretion of the investigator.~~	Clarifying language to prohibit concomitant use of strong CYP3A inhibitors and inducers
Section 9.3.2 Permitted Medications	~~Concomitant use of tolvaptan during the study is permitted if the criteria specified in Inclusion #10 are met. Patients previously treated with tolvaptan must have discontinued drug for at least 3 months prior to Screen A visit. Initiation of concomitant tolvaptan use during the study is not permitted.~~	Patients receiving concomitant Tolvaptan are excluded from study
Section 9.5 Randomization	Patients will be randomized 1:1 to either bardoxolone methyl or placebo. Randomization will be stratified by baseline eGFR category (30 to 60; 60 to 90) ~~and concomitant tolvaptan use at baseline (yes; no)~~.	Patients receiving concomitant Tolvaptan are excluded from study
Section 9.10 Study Procedures	A Central Laboratory should be used for all lab-based assessments. For specific guidance on lab sample collection, processing, and shipment, please refer to the Laboratory Reference Manual.	Clarification
Section 9.10.10 Vital Sign Measurements	For specific guidance related to blood pressure measurement, please see the Study Reference Manual.	Clarification

Section	Version 3	Rationale
[redacted]	[redacted]	Clarification
[redacted]	[redacted]	Clarification
[redacted]	[redacted]	Clarification
Section 12.1 Sample Size	With 300 patients enrolled, the study will have approximately 80% power to detect a ~~minimum detectable~~difference ~~(*i.e.*, at least 50% power)~~between the two treatment groups in change from baseline in eGFR of ~~1.6~~ 2.2 mL/min/1.73 m^2 ~~and at least 80% power to detect a difference of 2.3~~ at Week ~~52~~48. The power calculation, which was based on mixed-model repeated measures (MMRM) analysis, assumes the following: • ~~10~~9 repeated measurements (Weeks 1, 2, 4, 6, 8, 12, 24, 36, ~~48,~~ and ~~52)~~48); • The correlation between observations on the same subject is 0.7; • Two-sided Type I error rate of 0.05; • Standard deviation of change from baseline in eGFR of 8 mL/min/1.73 m^2; • Analyses are based on the intent-to-treat (ITT) population; • No imputation for missing data since all patients are included in MMRM analysis.	Clarification

Section	Version 3	Rationale
Section 12.1 Sample Size	Analysis of covariance (ANCOVA) will be used for analysis of the off-treatment endpoints (i.e., Week 52 and Week 104). Using a two-sample t-test to estimate power for the ANCOVA analysis, the study will have ~~at least~~ approximately 80% power to detect a difference between the two treatment groups in change from baseline in eGFR of 2.6 mL/min/1.73 m2 . The power calculation assumes the following: • Two-sided Type I error rate of 0.05; • Standard deviation of change from baseline in eGFR of 8 mL/min/1.73 m2; • Analyses are based on the intent-to-treat (ITT) population; • Missing data imputed using multiple imputation; • ANCOVA analysis expected to have approximately the same power as the t-test used for study planning. The method for maintaining strict control of the Type I error will be described in the statistical analysis plan (SAP). ~~Missing data will not be imputed for the primary analysis since all data collected will be included in the MMRM analysis.~~ Appropriate sensitivity analyses of the primary analysis will be specified in the SAP.	Clarification

Section	Version 3	Rationale
Section 12.3.1 Primary Analysis of Efficacy	~~The dependent variable~~ Mixed-model repeated measures (MMRM) analyses will be used to analyze the ~~primary and key secondary~~ on-treatment efficacy endpoints of change from baseline in eGFR at Week 48 and Week 100. 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 as a continuous covariate. Other covariates may be specified in the SAP. ~~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. Missing data will not be imputed for the primary analysis since all data collected will be included in the MMRM analysis. ~~Sensitivity analyses of the primary analysis will be specified in the SAP.~~ Appropriate sensitivity analyses will be performed and defined in the SAP. ~~The primary analyses of efficacy using an unstructured covariance structure is expected to have approximately the same power as the analysis with compound symmetry used for study planning.~~ Analysis of covariance (ANCOVA) will be used to analyze the off-treatment efficacy endpoints of change from baseline in eGFR at Week 52 and Week 104. The dependent variable will be change from baseline in eGFR. The model will include change from baseline in eGFR as the dependent variable and baseline eGFR as a continuous covariate. Other covariates may be specified in the SAP. The off-treatment endpoints assess the preserved drug benefit relative to placebo following withdrawal of treatment; therefore, analyses of these endpoints do not include eGFR values collected during treatment. Missing data are imputed for ANCOVA analyses using multiple imputation.	Clarification
Section 13.1 Study Monitoring	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~~R2): Good Clinical Practice: Consolidated Guideline and current standard operating procedures.	Updated ICH GCP Guidance
Section 14.4 Investigator Documentation	Before beginning the study, the principal investigator will be asked to comply with ICH E6(~~R1~~R2) 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	Updated ICH GCP Guidance

Section	Version 3	Rationale
Section 15.2 Ethical Conduct of the Study	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~~R2) [https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf~~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 [~~http://www.wma.net/en/30publications/10policies/b3/~~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.	Updated hyperlink
Section 15.3 Written Informed Consent	For sites outside of the United States, the signed consent will be obtained in accord with local regulations, ICH E6 (~~R1~~R2), and principles of the Declaration of Helsinki.	Updated ICH GCP Guidance
Section 18 References	~~Ratitch B, O'Kelly M, Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. Pharm Stat 2013;12:337-47.~~	Updated References

AMENDMENT CHANGE DOCUMENT
CLINICAL STUDY PROTOCOL 402-C-1808
Study Title: A Phase 3 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with Autosomal Dominant Polycystic Kidney Disease

Protocol History

Version 01	12 December 2018
Version 02	4 March 2019

Confidentiality Statement

SUMMARY OF CHANGES

The following document outlines the changes that have been made to Version 1 to produce the text of Version 2. Additionally, the following points are provided:

- New text that is added is marked with an underscore; text that has been deleted is marked with a ~~strikethrough~~.
- The changes made in the body of the protocol are reflected in the synopsis; the corresponding changes made in the synopsis are not described.
- Grammatical corrections and minor editorial changes are not described.
- Section numbers refer to the numbers in the new version of the protocol.

Section	Version 2	Rationale
Emergency Contact Information	[redacted] [redacted] Office: [redacted]	Updated personnel
Section 4 List of Abbreviations and Definitions of Terms	~~ESRD~~ ESKD End stage ~~renal~~ kidney disease	Updated abbreviation and term throughout entire text
Section 5.1.2.5 Hypomagnesaemia	Hypomagnesaemia has not been commonly reported in PH patients to date,	Clarification
[redacted]	[redacted]	Clarification
[redacted]	[redacted]	Clarification
Section 7.1 Overall Study Design	Patients with eGFR 60 to 90 mL/min/1.73 m^2 at screening should not comprise more than approximately 40% of enrolled patients.	Limited total enrollment of patients with higher baseline eGFR

Section	Version 2	Rationale
Section 8.1 Patient Inclusion Criteria	2. Diagnosis of ADPKD by modified Pei-Ravine criteria: 1) at least 3 cysts per kidney by sonography or at least 5 cysts by CT or MRI with family history of ADPKD or 2) at least 10 cysts per kidney by any radiologic method and exclusion of other cystic kidney diseases if without family history;	Clarification
Section 8.1 Patient Inclusion Criteria	3. Screening eGFR (average of Screen A and Screen B eGFR values) ≥ 30 ~~and~~ to ≤ 90 mL/min/1.73 m2 (18 to 55 years) or ≥ 30 ~~and~~ to ≤ 44 mL/min/1.73 m2 (56 to 70 years): a. Patients with either screening eGFR ≥ 60 to ≤ 90 mL/min/1.73 m^2 or age 56 to 70 years, must have evidence of ADPKD progression (i.e., eGFR decline of ≥ 2.0 mL/min/1.73 m^2 per year, based on historical eGFR data and medical monitor discretion); b. The two eGFR values collected at Screen A and Screen B visits used to determine eligibility must have a percent difference ≤ 25%;	Added requirement for evidence of ADPKD progression to ensure the population studied in the trial is one that is at risk of progression to ESKD
Section 8.1 Patient Inclusion Criteria	6. Adequate bone marrow reserve and organ function at the Screen A visit as follows: a. Hematologic: Absolute neutrophil count > 1.5 x 109/L, platelets > 100 x 109/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) ≤ the upper limit of normal (ULN)~~1.5X ULN~~;	Changed upper limit to require within normal limits
Section 8.1 Patient Inclusion Criteria	10. Concomitant use of tolvaptan during the study is permitted if the following criteria are met: a. Patient must have been receiving tolvaptan for at least 6 months prior to Screen A visit; b. Patient must be receiving stable dose of tolvaptan for at least 8 weeks prior to Screen A visit; c. ALT and AST must be within normal limits (≤ ULN) at Screen A visit; d. Patient has no history of elevations of ALT or AST > ULN while receiving tolvaptan; e. Tolvaptan dose is not expected to change or be stopped during the trial.	Added to inclusion requirements for patients currently receiving tolvaptan

Section	Version 2	Rationale
Section 8.2 Patient Exclusion Criteria	2. Patients previously treated with tolvaptan must have discontinued drug for at least 3 months prior to Screen A visit and had no history of elevations of ALT or AST > ULN while they were receiving tolvaptan. Initiation of concomitant tolvaptan use during the study is not permitted;	Added to exclusionary requirements for patients previously treated with tolvaptan
Section 8.5 Patient Discontinuation and Termination	Patients have the right to discontinue study drug or withdraw from ~~the~~ study follow-up at any time for any reason, without prejudice to their medical care. Furthermore, the investigator may discontinue a patient from study drug. Consultation with the medical monitor should occur prior to study drug discontinuation ~~or withdrawing a patient from the study~~.	Clarification
Section 8.5.1 Patient Study Drug Discontinuation Criteria	8.5.1. Patient Study Drug Discontinuation Criteria Study drug discontinuation refers to a patient's stopping administration of study drug. Reasons for study drug discontinuation may include the following: ~~The standardized disposition term is listed in BOLD and any associated details are listed in [brackets]:~~ ADVERSE EVENT; ~~[Occurrence of an AE or change in medical status that leads the investigator to be concerned about the patient's welfare];~~ DEATH; LOST TO FOLLOW-UP; PHYSICIAN DECISION; PROTOCOL SPECIFIED CRITERION MET; ~~STUDY TERMINATION BY SPONSOR [Sponsor termination of the study]~~ WITHDRAWAL BY SUBJECT ~~[Voluntary withdrawal]~~ PREGNANCY ~~[Females who become pregnant during the study]~~ ~~INVESTIGATOR UNBLINDING~~	Modified list of options for drug discontinuation reasons

Section	Version 2	Rationale
Section 8.5.1 Patient Study Drug Discontinuation Criteria	~~Patients should temporarily discontinue study drug, and the medical monitor should be contacted to discuss if permanent study drug discontinuation is required, 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%).~~	Removed duplicate information that is already described in protocol section 9.1.2
Section 8.5.1 Patient Study Drug Discontinuation Criteria	To minimize missing data, patients who are permanently discontinued from study drug should still continue with the study follow-up, completing all study visits and undergo all scheduled study assessments through Week 104, and undergo all scheduled study assessments, if possible. For patients who no longer wish to return for all study visits a number of follow-up options are available including: • Reduced in-person visit schedule; • Telephone contact only; • Non-direct follow-up of patient information including obtaining additional information from the patient's medical records (e.g., ES~~R~~KD or death). These reduced follow-up options should be discussed with theany patient considering study termination. Any discussions about reduced follow-up options must be documented in the patient's source file and discussed with the study manager.	Added follow-up options to minimize missing data following early discontinuation of study treatment.

Section	Version 2	Rationale
Section 8.5.2 Patient Study Termination Criteria	8.5.2 Patient Study Termination Criteria Study termination refers to a patient's stopping study ~~drug~~ follow-up, which includes ~~and all~~ study assessments, visits, and all contact with the site regarding the trial. Reasons for study termination include the following. ~~The standardized disposition term is listed in BOLD and any associated details are listed in [brackets]:~~ DEATH LOST TO FOLLOW-UP; WITHDRAWAL OF CONSENT BY SUBJECT ~~[Withdrawal of consent];~~ ~~PROTOCOL SPECIFIED WITHDRAWAL CRITERIA MET [ESRD (initiation of maintenance dialysis or kidney transplant)];~~ ~~STUDY TERMINATION BY SPONSOR [Sponsor termination of the study].~~	Modified list of reasons to terminate from the trial.
Section 8.5.2 Patient Study Termination Criteria	Every reasonable effort should be made to contact patients who do not return for a scheduled visit. Follow-up options described in Section 8.5.1 should be discussed with patients who no longer wish to return for all scheduled in person visits. Patients should not be considered lost to follow-up until the scheduled Week 104 visit date. The term "withdrawal of consent" should be used only when the patient no longer wishes to participate in the trial and no longer authorizes investigators to make efforts to continue to obtain their outcome data. The investigator should inquire about the reason for withdrawal of consent, request the patient return all unused investigational product, request the patient return for end-of-treatment and follow-up visits (if applicable), and follow-up with the patient regarding any unresolved AEs. ~~If a patient terminates from the study due to reaching ESRD (defined as the initiation of maintenance dialysis for 12 weeks or more or kidney transplant), the patient should complete an end of treatment visit and the investigator should record the ESRD event as an adverse event and document the date of dialysis initiation or kidney transplantation.~~	Clarification of follow-up expectations to minimize missing data.

Section	Version 2	Rationale
Section 9.1.1 Management of Fluid Status	Laboratory data and rapid weight gain will also be used to monitor fluid status after randomization. Patients who experience a BNP > 100 pg/mL that represents a doubling (or more) of BNP levels from Day 1 should have an unscheduled telephone contact immediately (see Section 9.10.15 for description of telephone contact). ~~If fluid retention is suspected, the patient must be instructed to stop taking study medication immediately and be medically evaluated by the investigator or a local physician within 1 to 2 days.~~ ~~Additionally, after randomization, patients will be closely monitored for rapid weight gain suggestive of fluid overload.~~ In addition, patients will be given a Sponsor-provided scale to use at home to collect and record their weights daily during the first 8 weeks of the treatment period and weekly thereafter. Patients who experience a five pound (2.3 kilogram) or greater increase in weight since their Day 1 weight during the first 8 weeks must have an unscheduled telephone contact immediately. Whether due to BNP elevations or weight gain, if clinically important fluid retention is suspected, the patient must be instructed to stop taking their study medication immediately and be medically evaluated by the investigator or a local physician within 1 to 2 days. Investigators are encouraged to consider starting or increasing doses of diuretics (thiazides, loop diuretics) early after recognition of edema. This can be done concurrently with temporary drug discontinuation and re-initiation. Patients may not restart their study medication until the investigator has completed and documented an assessment of fluid overload. 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 contact the clinic to assess the need for an unscheduled physical examination and laboratory assessment by the investigator. Study medication should not be discontinued unless clinically important fluid retention is suspected ~~until the investigator has completed and documented an assessment of fluid overload~~. If suspected, the patient must be instructed to stop taking their study medication immediately and be medically evaluated by the investigator or a local physician within 1 to 2 days.	Updated protocol for management of fluid status

Section	Version 2	Rationale
Section 9.1.1 Management of Fluid Status	Investigators should advise patients to watch for signs and symptoms of fluid overload. Patients should be informed to notify their physicians immediately if they experience swollen feet, chest pain, shortness of breath with mild exertion or while lying down, or other relevant symptoms. The investigator must immediately assess symptoms of fluid overload and determine appropriate medical management, as necessary, including whether stopping drug administration is required. ~~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.~~	Updated protocol for management of fluid status
Section 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. If ALT or AST levels reach approximately 2X ULN or more during dose escalation, the investigator should discuss with the medical monitor consideration of slowing titration or down-titrating. Check transaminase levels (as well as TBL, GGT, alkaline phosphatase (ALP), and International Normalized Ratio (INR)) within 48 to 72 hours if the following occurs: • ALT or AST levels > 3~~5~~X ULN. Repeat testing every 72 to 96 hours until transaminase levels are below 3~~5~~X the ULN for at least one week ~~or until the patient withdraws consent~~. Testing for patients not located near the investigator (such that it is not practical to return to the site at the required intervals) may be performed at a local lab and sent to the investigator and medical monitor for review, by approval from the medical monitor.	Updated criteria for management of elevated transaminase levels
Section 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 and should consult the medical monitor for appropriate measures. ~~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.~~	Updated protocol for management of urinary protein

Section	Version 2	Rationale
Section 9.1.8 Nausea	If symptoms do not resolve, dose de-escalation, with consultation of the medical monitor, may be reasonable ~~necessary~~.	Clarification
Section 9.1.9 End Stage Kidney Disease	Patients approaching end stage kidney disease (ESKRD) should be closely monitored by the investigator to fully characterize their progression. For patients with When eGFR is approximately ≤ 15.0 mL/min/1.73 m2 or less, initiate implementmore frequent follow-up to closely monitorof safety assessments (i.e., clinical chemistry (incl.uding eGFR), hematology, vital sign assessments (incl. weight), BNP and NT-proBNP). Similar frequent follow-up may also be implemented for Ppatients with eGFR approaching > 15.0 mL/min/1.73 m2 who, in the investigator's opinion based on the anticipated progression of their disease, may be approaching ESKDmay also initiate more frequent follow-up at the investigator's discretion. Patient follow-up should be, at least everyapproximatelyonce every 4 weeks (± 2 weeks)or more frequent as appropriate, until one of the following occurs: • Initiation of dialysis; • Receipt of transplant. Upon initiation of dialysis, study drug should be temporarily discontinued. Because laboratory and vital sign assessments can be affected by receiving dialysis, those safety assessments should not be performed concurrently while a patient is receiving dialysis. Patients receiving dialysis should continue to be followed for vital status and SAEs by phone or in-person according to the protocol scheduled visits. Dialysis not lasting at least 12 weeks will be considered acute dialysis, and patients should be considered for re-initiation of study drug with medical monitor approval. Such patients should continue to undergo frequent follow-up (i.e., at least once every 4 weeks (± 2 weeks)) while eGFR ≤ 15.0 mL/min/1.73 m2. Study drug may be re-started following acute dialysis, with medical monitor approval. Dialysis lasting at least 12 weeks will be consideredconfirmed as maintenance dialysis. Upon confirmation of maintenance dialysis, study drug should be permanently discontinued. ESKD should be considered an important medical event, and as such recorded as an SAE.	New section. Added protocol for management of ESKD.

Section	Version 2	Rationale
Section 9.1.9 End Stage Kidney Disease	Upon receipt of kidney transplant, study drug should be permanently discontinued. Following permanent study drug discontinuation due to confirmation of maintenance dialysis or receipt of kidney transplant, patients reaching ESKRD should continue to be followed only for vital status and SAEs approximately quarterly by phone or in-person according to the planned contact schedule in Section 7.5 through the end of the trialtheir scheduled Week 104 visit date. Follow-up should be limited to vital status and SAEs. See Section Section 8.5 for description of follow-up options following permanent study drug discontinuation. Initiation of dialysis (acute and/or maintenance) and receipt of kidney transplant due end stage kidney disease should be considered important medical events, and as such recorded as SAEs.	(Continued) New section. Added protocol for management of ESKD.
Section 9.3.1 Excluded Medications	When concomitant use of a CYP3A4 inhibitor is unavoidable, patients should be carefully monitored. If a strong CYP3A4 inhibitor is medically necessary ~~warranted~~, the study drug dose ~~should~~ may be reduced or ~~study drug should be~~ temporarily discontinued at the discretion of the investigator.	Clarification
Section 9.3.2 Permitted Medications	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.~~	Clarification
Section 9.5 Randomization	An IWRS will be utilized to randomize patients 1:1 to bardoxolone methyl or placebo. Randomization will be stratified by baseline eGFR category (30 to 60; 60 to 90) and concomitant tolvaptan use at baseline (yes; no).	Clarification. Added stratification imformation also referenced in Section 7.1.
Section 9.6.1 Patient Unblinding	Patients must permanently discontinue taking study drug if their treatment assignment has been unblinded to the investigator (or designee). Such patients must undergo the same study drug discontinuation procedures as those patients who discontinue taking study drug for other reasons. Following permanent study drug discontinuation due to patient unblinded, patients should continue with study follow-up through their scheduled Week 104 visit date for vital status only.	Updated protocol for patient unblinding

Section	Version 2	Rationale
Section 9.7 Unscheduled Visits	Unscheduled visits are allowed for the following reasons: • Assessment of weight gain per Section 9.1.1; • Management of an AE or SAE; • Performance of additional laboratory tests for clinically abnormal laboratory test values or to confirm a possible pregnancy; • Dose re-escalation; • Dose de-escalation; • eGFR ≤ 15 per Section 9.1.9 ; • Any time the investigator feels that it is clinically appropriate for patient safety.	Added to list of reasons for unscheduled visits
Section 9.10.11 Physical Examination	Clinically significant findings at Screening must be ~~recorded as~~ addressed in medical history, (i.e., findings should be attributable to a diagnosis recorded in medical history).	Clarification
Section 9.10.13 Study Drug Administration	Study drug administration (IP) should be recorded in a patient diary at least through Week 12.	Clarification
Section 9.10.18.1 eGFR	~~The equation used to calculate eGFR for each patient throughout the study will be based on the patient's age on the date of consent.~~ The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation will be used: eGFR (mL/min/1.73 m2) = 141 × min(Scr/κ, 1)α × max(Scr/κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black] Where Scr is serum creatinine (mg/dL), κ is 0.7 for females or 0.9 for males, and α is -0.329 for females or -0.411 for males. Min indicates the minimum of Scr/κ or 1 and max indicates the maximum of Scr/κ or 1. Age indicates age at time of lab collection.	Clarification of eGFR calculation methodology

Section	Version 2	Rationale
Section 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~~ the last study follow-up visit, regardless of the relationship of the AE to study drug.	Expanded AE reporting window to extend throughout study follow-up, irrespective of date of last dose.
Section 11.7 Reporting Serious Adverse Events	Note that the following SAEs which are commonly observed in this patient population as part of CKD progression will not be reported to regulatory authorities as individual expedited reports, except in unusual circumstances. • Initiation of dialysis ~~Dialysis~~ due to end stage kidney disease ~~Hypotension~~ • Kidney transplant due to end stage kidney disease • ~~Hyperkalemia~~ • ~~Fatigue~~ 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.	Updated SAE reporting guidelines for specified events due to CKD disease progression.