COVER PAGE

Official Title:	An Extended Access Program to Assess Long Term Safety of Bardoxolone Methyl in Patients With Chronic Kidney Disease (EAGLE)
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AN EXTENDED ACCESS PROGRAM TO ASSESS LONG TERM SAFETY OF BARDOXOLONE METHYL IN PATIENTS WITH CHRONIC KIDNEY DISEASE (EAGLE)

VERSION 4.0 - 09 NOVEMBER 2022

Protocol History

Version 4.1 Japan – 09 Nov 2022
Version 3.1 Japan – 16 Sep 2021
Version 3.0 – 30 Jun 2020
Version 2.0 – 31 Jan 2019
Version 1.0 – 04 Sep 2018

SPONSOR APPROVAL AND SIGNATURE PAGE

{See Appended Electronic Signature Page}

[redacted], MD, MPH, MBA

Date

{See Appended Electronic Signature Page}

[redacted]

Date

{See Appended Electronic Signature Page}

[redacted]

Date

{See Appended Electronic Signature Page}

[redacted]

Date

INVESTIGATOR'S AGREEMENT

I have read the 402-C-1803 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, MPH, MBA [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] Facsimile: [redacted] [redacted] E-mail: [redacted]	

2. SYNOPSIS

Name of Sponsor/Company:
Reata Pharmaceuticals, Inc.

Name of Investigational Product:
Bardoxolone methyl

Title of Study:
An Extended Access Program to Assess Long Term Safety of Bardoxolone Methyl in Patients with Chronic Kidney Disease

Study center(s): Approximately 230 study centers

Studied period: Until commercial availability of bardoxolone methyl for each indication and region. Actual date first patient first visit: March 2019 Estimated date last patient completed: Patient will remain in the study until bardoxolone methyl is available through commercial channels or until patient withdrawal, whichever is sooner The end of the study is defined as the last visit of the last patient.	**Phase of development:** 3a

Primary Objectives: To provide continuing open-label treatment with bardoxolone methyl as part of this extended access program while collecting ongoing safety and tolerability data of bardoxolone methyl.

Safety Endpoints: Frequency, intensity, and relationship to study drug of adverse events (AEs) and serious adverse events (SAEs) and change from baseline in the following assessments: physical examinations, vital sign measurements, weight, urine albumin to creatinine ratio (ACR), and laboratory results.

Methodology:

This extended access study will assess the long-term safety and tolerability of bardoxolone methyl in qualified patients with chronic kidney disease (CKD) who previously participated in a qualifying, clinical study with bardoxolone methyl. The CARDINAL study (402-C-1603, NCT03019185, EudraCT 2016-004395-22) and FALCON study (402-C-1808, NCT03918447, EudraCT 2018-004651-20) are the only qualifying clinical studies at this time.

The Day 1 visit of EAGLE is not required to be the same day as the End of Study visit of the prior qualifying study. Lab assessments from the qualifying study will be used for EAGLE eligibility and maximum treatment dose assignment (Week 100 for CARDINAL or FALCON protocol versions 1 through 5, and Week 108 [B] for FALCON versions 6 and newer) if those assessments were done ≤ 8 weeks before Day 1. In the event that the eligibility lab assessments were obtained > 8 weeks before the planned EAGLE Day 1 visit, a screening visit will be required for EAGLE enrollment.

The maximum bardoxolone methyl dose will be determined by the proteinuria status based on the ACR value from the eligibility lab assessments from the prior qualifying study, or for patients requiring a screening visit, the maximum bardoxolone methyl dose will be determined based on the ACR values from the screening labs. Patients with ACR ≤ 300 mg/g will be titrated to a maximum dose of 20 mg,

and patients with ACR > 300 mg/g will be titrated to a maximum dose of 30 mg. Adult patients (≥ 18 years of age) 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 eligibility ACR > 300 mg/g) unless contraindicated clinically and approved by the medical monitor. Patients under the age of 18 enrolling from CARDINAL will start dosing at 5 mg every other day during the first week (from Day 1 through the Week 1 visit) and begin once-daily dosing with 5 mg during the second week of the study (following the Week 1 visit through the Week 2 visit), and then continue with once-daily dosing following the same aforementioned dose-titration scheme based on eligibility ACR at Weeks 2, 4, and 6. Patients under the age of 18 enrolling from FALCON will follow the adult dose titration schedule. Dose de-escalation is permitted during the study if indicated clinically, and subsequent dose re-escalation is also permitted.

All patients in the study will follow the same visit and assessment schedule. Patients will be scheduled to be assessed in person during treatment at Day 1, Weeks 1, 2, 4, 6, 8, 12, 24, and every 24 weeks thereafter. Patients will also be assessed by telephone contact on Days 3, 10, 21, 31, 38, and 45. If the Day 1 visit for EAGLE is the same as the end-of-study visit for CARDINAL (all versions) or FALCON (protocol version 5 and older), the laboratory assessments required for both visits should only be completed once. If the Day 1 visit for EAGLE is the same as the end-of-study visit for FALCON (protocol version 6 and newer), the lab assessments required for both visits should be completed for each study individually. If the Day 1 visit of EAGLE is not on the same day as the end-of-study visit from prior qualifying study, lab assessments will be performed for Day 1 through the EAGLE central lab.

The conduct of the study, according to protocol specifications, was impacted by the COVID-19 pandemic. As a result, and as of Version 3 of the protocol, modifications intended to address access to and administration of investigational product, and adherence to protocol-specified visits and laboratory assessments were implemented. These modifications are described in Appendix 1 (COVID-19 Mitigations).

Number of patients (planned):

Patient numbers will be determined by those who are currently participating or have previously participated in a qualifying clinical study with bardoxolone methyl.

Main criteria for inclusion:

1. Patients who are participating (or who have participated) in qualifying studies and who have not been required to discontinue study treatment for protocol or safety reasons and who have completed required End-of-Treatment and/or Follow-up visits in a prior clinical study with bardoxolone methyl and who, according to the assessment of the investigator, have a potential positive benefit-risk assessment for participating in the trial.
2. Meets the following eligibility criteria based on assessments from the prior qualifying study or from a screening visit, if applicable.
    a. Not expected to reach end stage kidney disease (ESKD) or nephrotic syndrome within 12 weeks of study enrollment, in the investigator's judgement; subjects with eGFR < 20 ml/min/1.73m^2 should be discussed with the medical monitor before enrollment (eg, such subjects with an average rate of eGFR decline > 1.0 ml/min/1.73m^2 per month in the 3 months prior to eligibility assessment may not be eligible);
    b. BNP < 200 pg/mL at the last on-treatment visit in the prior qualifying study or at a new screening visit, if applicable.
    c. No occurrence of a cardiovascular serious adverse event in the prior qualifying study or in the interval between the end of the qualifying study and the screening visit, if applicable.
3. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures;
4. Evidence of a personally signed and dated informed consent document (and assent form if necessary) indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study prior to initiation of any protocol-mandated procedures.

Major exclusion criteria:

1. Participation in other investigational clinical studies involving interventional products being tested or used in a way different from the approved form or when used for an unapproved indication;
2. Patients who have an ongoing SAE from a clinical study that is assessed by the investigator as related to bardoxolone methyl;
3. Unwilling to practice acceptable methods of birth control (both males who have partners of childbearing potential and females of childbearing potential) while screening, taking study drug, and 30 days after the last study drug dose;
4. Women who are pregnant or breastfeeding;
5. 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;
6. Known hypersensitivity to any component of the study drug.

Investigational product, dosage, and mode of administration:

Bardoxolone methyl will be administered at oral doses of 5, 10, 20, or 30 mg

Reference therapy, dosage, and mode of administration:

None.

Criteria for evaluation:

Safety: Results of physical examination, laboratory results, ACR, vital sign measurements, weight, AEs, and SAEs.
Statistical methods: Sample size: The aim of this long-term extended access study is primarily to provide continuing bardoxolone methyl treatment to patients and to assess long-term safety and tolerability hence no single primary variable has been identified. Patient numbers will be determined by those who are participating (or who have previously participated) in a qualifying clinical study with bardoxolone methyl. Primary analysis of safety: As the extension is an open-label design with no comparator group, all statistical analyses will be descriptive. The summary tables will be presented for the overall group of patients, and also split by previous treatment groups (ie, bardoxolone methyl or placebo) in prior bardoxolone methyl clinical studies.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ACE	angiotensin converting enzyme
ACR	albumin to creatinine ratio
ADPKD	autosomal dominant polycystic kidney disease
AE	adverse event
ALT	alanine aminotransferase
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
BMI	body mass index
BNP	B-type natriuretic peptide
BUN	blood urea nitrogen
CFR	Code of Federal Regulations (US)
CKD	chronic kidney disease
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ERA	Endothelin Receptor Antagonist
ESKD	end stage kidney disease
FDA	Food and Drug Administration (US)
GCP	good clinical practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transpeptidase
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IP	investigational product
IRB	Institutional Review Board
Nrf2	nuclear factor erythroid 2-related factor 2
NT-proBNP	N-Terminal prohormone B-type natriuretic peptide
PH	pulmonary hypertension
SAE	serious adverse event

Abbreviation or Specialist Term	Explanation
T2D	type 2 diabetes
ULN	upper limit of normal
US	United States
WOCBP	women of childbearing potential

5. INTRODUCTION

Bardoxolone methyl and its analogs are oleanolic acid-derived synthetic triterpenoid compounds that potently induce the nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2) – Kelch-like ECH-associated protein 1 (Keap1) pathway (Wu, 2011; Rojas-Rivera, 2012). Through interaction with the Nrf2 repressor molecule, Keap1, bardoxolone methyl and its analogs promote translocation of Nrf2 to the nucleus, where Nrf2 binds to antioxidant response elements in the promoter region of its target genes, leading to induction of many antioxidants and cytoprotective enzymes and related proteins (Lee, 2009; Dinkova-Kostova, 2005). Bardoxolone methyl and its analogs are also potent inhibitors of the nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB) inflammatory pathway through both direct (ie, inhibition of the inhibitor of nuclear factor kappa β kinase beta subunit [IKKβ] kinase activity) and indirect mechanisms (ie, detoxification of reactive oxygen species) (Osburn, 2008). Because of this dual mechanism of action, bardoxolone methyl and its analogs are hypothesized to have potential therapeutic relevance in a variety of disease settings involving oxidative stress and inflammation.

Multiple studies validate the renal protective effect of Nrf2 activation. In contrast, Nrf2 gene ablation intensifies inflammation, oxidative stress, and renal injury in preclinical models. Nrf2-knockout mice exhibit a lupus-like autoimmune nephritis (Yoh, 2001) and histologic analyses of kidney tissue show enlarged glomeruli, mesangial cell proliferation, thickening of the glomerular basement membrane, and glomerulosclerosis (Ma, 2006). Similarly, Nrf2-knockout mice are more susceptible to nephrotoxic insults and develop more severe renal impairment. Mechanistic studies demonstrate that Nrf2-mediated protection against these effects is at least partially through inhibition of transforming growth factor-β1 and reduction of extracellular matrix production (Jiang, 2014). Collectively, these data establish that Nrf2 plays an important role in maintaining the function and structure of the kidney and Nrf2 activation offers protection from renal injury and dysfunction.

Chronic kidney disease (CKD) is a disease of decreased kidney function that can progress to kidney failure and end-stage kidney disease (ESKD). Although GFR decline can be initiated by different pathogenic stimuli, the pathogenic role of inflammatory processes in disease progression and declining renal function is similar across different forms of CKD. For example, genetic defects in the glomerular basement membrane in Alport syndrome, hypoglycemia in type 1 diabetes (T1D), abnormal immunoglobulin A (IgA) deposition and clearance in IgA nephropathy (IgAN), segmental scarring in focal segmental glomerulosclerosis (FSGS), and renal cyst formation in autosomal dominant polycystic kidney disease (ADPKD), all trigger a cascade of pathological inflammatory processes that, over prolonged periods, result in oxidative stress, mesangial matrix expansion, glomerulosclerosis and fibrosis, decreased surface area for filtration, and reduced renal function.

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

mediated activation of inflammatory pathways leads to fibrosis, promoting structural alterations in the mesangium and glomerular basement membrane thickening that contributes to GFR decline. GFR decline from these processes inevitably leads to ESKD.

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

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

The profile of eGFR increases with bardoxolone methyl reflects its multiple protective and anti-inflammatory effects. Early improvements in eGFR evident within the first 4 weeks of bardoxolone methyl treatment are likely attributed to the reversal of acute 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 T2D CKD have been treated with bardoxolone methyl for 1 year or longer, with no evidence of renal toxicity, as assessed by validated markers of renal injury, proportion of patients with clinically meaningful loss of eGFR, renal serious adverse events (SAEs) and ESKD. Thus, the collective data support that bardoxolone methyl may have disease-modifying effects in the kidney (eg, reversal of mesangial expansion and interstitial fibrosis) that are beneficial and not deleterious. On the basis of these results, bardoxolone methyl is currently being evaluated in a Phase 2/3 study in patients with Alport syndrome and in a Phase 2 study in patients with CKD due to T1D, IgAN, ADPKD, or FSGS.

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

5.1. Clinical Experience with Bardoxolone Methyl

Overall, bardoxolone methyl has been tested in multiple CKD studies enrolling almost 6000 patients, and approximately 3,700 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 ESKD (need for chronic dialysis, renal transplantation, or renal death) or cardiovascular death. Similar to prior studies, bardoxolone methyl patients had mean increases in eGFR that occurred by Week 4 of treatment and remained above baseline through Week 48 (overall mean increase of 5.5 mL/min/1.73 m^2). In contrast, placebo-treated patients experienced a mean decline in eGFR (–0.9 mL/min/1.73 m^2, 95% CI –1.2 to –0.5 mL/min/1.73 m^2), corresponding to a relative difference between groups of 6.4 mL/min/1.73 m^2 (95% CI 5.9 to 6.9 mL/min/1.73 m^2, $p<0.001$) (de Zeeuw, 2013).

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

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

Study	Phase/ Country	Study Design	Study Population	# of Patients	Treatment Duration	Placebo-corrected ΔeGFR (mL/min/1.73m^2)[1]
CKD Studies						
402-C-0801 (Stratum 1)	2a/ US	Multicenter, Open-Label, Dose-Ranging, Randomized	Age >=18, Diabetic nephropathy	60	28 days	6.7[2] (p<0.001)
402-C-0801 (Stratum 2)	2b/ US	Multicenter, Open-Label, Dose-Ranging, Randomized	Age >=18, Diabetic nephropathy	20	56 days	7.2[2] (p<0.001) CrCl also sig. increased
402-C-0804 (BEAM)	2/ US	Multicenter, Double-Blinded, Randomized, Placebo-Controlled	Age >=18, T2D and CKD	227	52 weeks	8.6 at WK52 (p<0.001 vs PBO)
402-C-0902	2/ US	Multicenter, Open-Label, Randomized, Parallel-Group, Dose-Ranging	Age >=18, T2D and CKD	131	85 days	6.5[2] (p<0.001)
402-C-0903 (BEACON)	3/ Global	Multinational, Multicenter, Randomized, Double-Blinded, Placebo-Controlled	Age >=18, T2D and Stage 4 CKD	2185	Median: 7 months with 522 patients through Week 48	6.4 (p<0.001 vs PBO) CrCl also significantly increased
402-C-1102	1/US	Multi-Dose, Multicenter, Open-Label	Age>=18, T2D and Stage 3b and 4 CKD	24	56 days	9.0 (p<0.05)
RTA402-005 (TSUBAKI)	2/ Japan	Randomized, Double-Blinded, Placebo-Controlled	Age >=20, T2D and Stage 3 and 4 CKD	120	16 weeks	6.6 (inulin GFR) (p=0.008 vs PBO)
402-C-1603	2/US	Multicenter, Open-label	Age 12 to 65, Alport syndrome	30	48 weeks	10.4 (p<0.001)

402-C-1603 Year 1	3/Global	Randomized, Double-Blinded, Placebo-Controlled	Age 12 to 70, Alport Syndrome	157	48 weeks	9.5 (p<0.001 vs PBO)
402-C-1702	2/US	Multicenter, Open-label	Age ≥ 18, ADPKD	31	12 weeks	9.3 (p<0.001)
402-C-1702	2/US	Multicenter, Open-label	Age 18 to 70, IgA Nephropathy	26	12 weeks	8.0 (p<0.0001)
402-C-1702	2/US	Multicenter, Open-label	Age 18 to 70, T1D CKD	28	12 weeks	5.5 (p=0.025)
402-C-1702	2/US	Multicenter, Open-label	FSGS	18	12 weeks	7.8 (p=0.003)
Non-CKD Studies						
402-C-0501	1/ US	Open-label, Dose-escalation	Age >=18, Advanced Solid Tumors or Lymphoid Malignancies	47	Median: 56 days	18.2[2] (p<0.0001)
402-C-0702	½/ US	Double-Blinded, Randomized	Pancreatic Cancer	34	Median: 56 days	32.2[2] (p=0.001)
402-C-1302 (LARIAT)	2/ US	Randomized, Double-Blinded, Placebo-Controlled	Age 18 to 75 PH (Baseline eGFR 82 mL/min/1.73 m^2)	54[3]	16 weeks	14.7 (p<0.001 vs PBO)

Abbreviations: ADPKD= autosomal dominant polycystic kidney disease; CKD=chronic kidney disease; CrCl=creatinine clearance; IgA=immunoglobulin A; eGFR=estimated glomerular filtration rate; FSGS=focal segmental glomerulosclerosis; PBO=placebo; PH=pulmonary hypertension; T1D=type 1 diabetes; T2D=type 2 diabetes; US=United States; Wk=week

[1] Unless noted, data are differences between mean eGFR changes from baseline for bardoxolone methyl versus placebo groups and p-values calculated comparing the difference in means between bardoxolone methyl and placebo groups.

[2] 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.

[3] Number of patients enrolled Cohorts 1 and 2.

5.1.2. Safety and Tolerability

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

5.1.2.1. Fluid Overload

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

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

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 reabsorption 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. Growth and Development (Weight and Height) in Adolescents

In study 402-C-1603 (CARDINAL) phase 3, due to the small number of patients and baseline differences in mean height and weight (placebo vs. bardoxolone methyl treated), a firm conclusion regarding effect on height and weight cannot be derived.

In study 402-C-1603, a total of 23 adolescent patients (ages 12-17 years) with Alport syndrome 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 body mass index (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).

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: n=68).

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objectives

- To provide continuing open-label treatment with bardoxolone methyl as part of this extended access program while collecting ongoing safety and tolerability data of bardoxolone methyl.

6.2. Primary Safety Endpoints

- Frequency, intensity, and relationship to study drug of AEs and SAEs and change from baseline in the following assessments: physical examinations, vital sign measurements, weight, urine albumin to creatinine ratio (ACR), and laboratory results.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This extended access study will assess the long-term safety and tolerability of bardoxolone methyl in qualified patients with CKD who previously participated in a qualifying clinical study with bardoxolone methyl. The CARDINAL study (402-C-1603, NCT03019185, EudraCT 2016-004395-22) and FALCON study (402-C-1808, NCT03918447, EudraCT 2018-004651-20) are the only qualifying clinical studies at this time.

The Day 1 visit of EAGLE is not required to occur on the same day as the End of Study visit of the prior qualifying study. Lab assessments from the qualifying study may be used for EAGLE eligibility and maximum treatment dose assignment (Week 100 for CARDINAL or FALCON protocol versions 1.0 through 5.0, and Week 108 [B] for FALCON protocol versions 6.0 and newer) if those assessments were done ≤ 8 weeks before Day 1. In the event the eligibility lab assessments were obtained > 8 weeks before the planned Day 1 EAGLE visit, a screening visit will be required for EAGLE enrollment.

Table 4 clarifies potential situations with patient eligibility.

Table 4: Lab Assessments for Eligibility

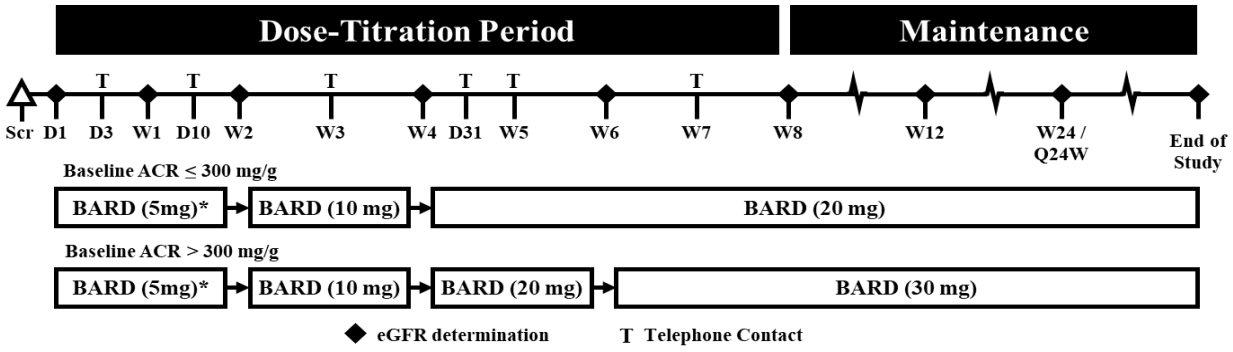
Patients Enrolling from CARDINAL or FALCON	
Day 1 of EAGLE Study	**Lab Assessments for Eligibility**
Day 1 is equal to end-of-study visit from the prior qualifying study	Week 100 for CARDINAL or FALCON protocol versions 1.0 through 5.0 Week 108 (B) for FALCON versions 6.0 and newer
Day 1 is ≤ 8 weeks after the eligibility lab assessments from the prior qualifying study	Week 100 for CARDINAL or FALCON protocol versions 1.0 through 5.0 Week 108 (B) for FALCON versions 6.0 and newer
Day 1 is > 8 weeks after the eligibility lab assessments from the prior qualifying study	A screening visit is required, and these lab assessments will be used for eligibility

The maximum bardoxolone methyl dose will be determined by proteinuria status based on the ACR value from the eligibility lab assessments from the prior qualifying study, or for patients requiring a screening visit, the maximum bardoxolone methyl dose will be determined based on the ACR values from the screening labs. Patients with eligibility ACR ≤ 300 mg/g will be titrated to a maximum dose of 20 mg, and patients with eligibility ACR > 300 mg/g will be titrated to a maximum dose of 30 mg. Adult patients (≥ 18 years of age) 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 eligibility ACR > 300 mg/g) unless

contraindicated clinically and approved by the medical monitor. Patients under the age of 18 enrolling from CARDINAL will start dosing at 5 mg every other day during the first week (from Day 1 through the Week 1 visit) and begin once-daily dosing with 5 mg during the second week of the study (following the Week 1 visit through the Week 2 visit), and then continue with once-daily dosing following the same aforementioned dose-titration scheme based on eligibility ACR at Weeks 2, 4, and 6. Patients under the age of 18 enrolling from FALCON will follow the adult dose titration schedule. Dose de-escalation is permitted during the study if indicated clinically, and subsequent dose re-escalation is also permitted.

All patients in the study will follow the same visit and assessment schedule, as outlined in the study schema (Figure 1). Patients will be scheduled to be assessed in person during treatment at Day 1, Weeks 1, 2, 4, 6, 8, 12, 24, and every 24 weeks thereafter. Patients will also be assessed by telephone contact on Days 3, 10, 21, 31, 38, and 45. If the Day 1 visit for EAGLE is the same as the end-of-study visit from the prior qualifying study, the assessments required for both visits should only be completed once. If the Day 1 visit of EAGLE is not on the same day as the end-of-study visit from prior qualifying study, lab assessments will be performed for Day 1 through the EAGLE central lab.

Figure 1: Schema for Study 402-C-1803



Abbreviations: ACR=albumin to creatinine ratio; D=day; W=week; eGFR=estimated glomerular filtration rate; Scr=screening

*Patients enrolling from CARDINAL (402-C-1603) that are under the age of 18 will receive bardoxolone methyl *every other day during Week 1.* Patients enrolling from FALCON (402-C-1808) that are under the age of 18 will receive bardoxolone methyl *every day during Week 1*

Note: Screening visit will be scheduled for subjects whose last lab assessments are more than 8 weeks old. Refer to Section 8.3 for additional details. Subjects requiring a screening visit will be consented on the same visits

The conduct of the study, according to protocol specifications, was impacted by the COVID-19 pandemic. As a result, and as of Version 3 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).

7.2. Number of Patients

Patient numbers will be determined by those who are participating and have previously participated in a qualifying clinical study with bardoxolone methyl.

7.3. Treatment Assignment

All patients will receive bardoxolone methyl in this study.

7.3.1. Dose Escalation

Adult patients (≥ 18 years of age) 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 eligibility ACR > 300 mg/g) unless contraindicated clinically and approved by the medical monitor. Patients from the CARDINAL study under the age of 18 at the time of consent for participation in the EAGLE study will start dosing at 5 mg every other day during the first week (from Day 1 through the Week 1 visit) and begin once-daily dosing with 5 mg during the second week of the study (following the Week 1 visit through the Week 2 visit), and then continue with once-daily dosing following the same aforementioned dose-titration scheme based on eligibility ACR at Weeks 2, 4, and 6. Patients from the FALCON study under the age of 18 at the time of consent for participation in the EAGLE study will follow the adult dose titration schedule. Dose escalation may proceed slowly if the patient experiences early elevation in ALT/AST over ULN eg, at Week 2 (See Section 9.1.2). The dosing objective is to titrate patients to the maximum dose determined by eligibility 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.

7.3.2. Dose De-Escalation and Re-Escalation

The investigator may choose to decrease the patient's dose to the prior dose (eg, 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, in-clinic visit within 4 weeks (± 3 days) to perform the assessments detailed in Section 9.6.

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 (± 2 days) after dose re-escalation and an unscheduled, in-clinic visit 2 weeks (± 3 days) after dose re-escalation to perform the assessments detailed in Section 9.6.

Patients who had a delayed initial dose-escalation should also have a telephone call 1 week (± 2 days) after each dose escalation and an in-clinic visit 2 weeks (± 3 days) after dose escalation to perform the assessments detailed in Section 9.6. If these timepoints no longer coincide with scheduled study visits, unscheduled phone calls and in-clinic visits should occur. These do not replace the regularly scheduled study visits; they should be performed as well.

7.3.3. Interruption and Resuming 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 refers to a *temporary* halt of study drug administration. If there are any questions regarding study drug interruption, please consult the medical monitor.

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 (eg, 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 does, 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 (eg, 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 approximately 1 week after resuming and an unscheduled, office visit 2 weeks (± 3 days) after resuming study drug to perform assessments detailed in Section 9.6.

7.3.4. Adolescent Dosing Rationale

Adolescents (12 ≤ age < 18) enrolling from FALCON 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 CARDINAL and EAGLE, approximately 20 adolescent patients with Alport syndrome 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.

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, T2D 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 CARDINAL), 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.

7.4. End of Study and Commercial Availability

Each patient will complete an End of Study visit that should occur within 30 days after bardoxolone methyl becomes available to the patient through commercial channels. Commercial availability is defined as when the commercial drug is approved for use by the relevant regulatory authority and is made available through commercial channels to that patient. The timing of commercial availability can vary by country, site and/or patient, depending on these factors. The scheduled study visits and IP dispensation will continue for each patient until commercial availability or alternative drug supply arrangements are made. More information on other scenarios for study closure are included in Section 7.5.

7.5. Criteria for Study Termination

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

7.6. Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of good clinical practice (GCP), protocol, or contractual agreement with Sponsor or the site is unable to ensure adequate performance of the study.

7.7. Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Sites

In the event that the Sponsor, an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), or regulatory authority elects to terminate or suspend the study or the

participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor.

7.8. Schedule of Assessments

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

Table 5: Schedule of Assessments

Assessment / Study Week (Day±Days)	Screening Visit[a]	Day 1[a,c]	Week 1 (Phone) Day 3 ± 2 Days	Week 1Day 7 ± 3 Days	Week 2 (Phone) Day 10 ± 2 Days	Week 2Day 14 ± 3 Days	Week 3 (Phone) Day 21 ± 2 Days	Week 4Day 28 ± 3 Days	Week 4 (Phone) Day 31 ± 2 Days	Week 5 (Phone) Day 38 ± 2 Days	Week 6 Day 42 ± 3 Days	Week 7 (Phone) Day 45 ± 2 Days	Week 8 Day 56 ± 3 Days	Week 12 Day 84 ± 3 Days	Week 24 ± 3 Days, Every 24 Weeks ± 3 Days	End of Study Visit[b]
Informed consent	X[c]	X[c]														
Inclusion/Exclusion	X	X														
Demographics[d]	X	X														
Prior and Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History	X	X														
Height	X	X		X		X		X			X		X	X	X	X
Weight at home		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight in-clinic	X	X		X		X		X			X		X	X	X	X
Dispense Weight & Study Drug Diary		X				X		X			X		X	X	X	
Collect/Review Weight & Study Drug Diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital sign measurements	X	X		X		X		X			X		X	X	X	X
Physical examination	X	X		X		X		X			X		X	X	X[e]	X[e]
Pregnancy test[f]		X													X	
Dispense study drug		X				X		X			X		X	X	X	
Collect study drug						X		X			X		X	X	X	X
Telephone contact			X		X		X		X	X		X				
Adverse event collection		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Basic Lipid Panel		X													X	X
Clinical Chemistries (incl. eGFR)[g]	X	X		X		X		X			X		X	X	X	X
BNP and NT-Pro BNP	X	X		X		X		X			X		X	X	X	X
Hematology	X	X		X		X		X			X		X	X	X	X
Urine collection for ACR[h]	X	X						X					X	X	X	X
Tanner Staging[i]		X													X	X

Abbreviations: AE=adverse event; BNP=B-type natriuretic peptide; eGFR=estimated glomerular filtration rate; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; ACR=albumin to creatinine ratio; WOCBP=women of child-bearing potential

[a] A screening visit will be conducted for subjects whose planned EAGLE Day 1 visit is not within 8 weeks of the eligibility lab assessments from the prior qualifying study. Refer to Section 7.1 for additional details. Subjects requiring a screening visit will be consented prior to the start of any screening assessments. All other subjects will be consented at the start of the Day 1 visit, before any procedures are performed for this, or the prior study.

[b] After the Week 24 visit, subjects will continue to be assessed in person every 24 weeks until the study ends. The End -of- Study visit should occur within 30 days after bardoxolone methyl becomes available to the subject through commercial channels. For additional details, see Section 7.4. Subjects who will be discontinued from the study prior to commercial availability of bardoxolone methyl must also complete all End-of-Study assessments as soon as possible (if possible, within 30 days of discontinuation).

[c] On Day 1, all procedures should be performed before study drug administration. AE assessment on Day 1 should be performed following study drug administration. If the Day 1 visit for EAGLE is the same as the end-of-study visit for CARDINAL (all versions) or FALCON (protocol version 5 and older), the laboratory assessments required for both visits should only be completed once.
If the Day 1 visit for EAGLE is the same as the end-of-study visit for FALCON (protocol version 6 and newer), the lab assessments required for both visits should be completed for each study individually.
[d] Demographics are to be performed on the earliest study visit, whether it be Day 1 or a Screening visit, if necessary.
[e] Assessment should include a complete physical examination as described in Section 9.9.7.
[f] A serum pregnancy test will be performed 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 health authorities or IRBs/IECs.
[g] eGFR will not be calculated by the central lab.
[h] Urine albumin to creatinine ratio will be measured by first morning void spot urine collection. Appropriate containers for the collection will be provided to the subject at the visit prior to collection.
[i] Adolescent patients from the FALCON (402-C-1808) ($12 \leq$ age < 18 years at consent) will be assessed by Tanner staging at all specified timepoints.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Inclusion Criteria

Diagnosis and main criteria for inclusion:

1. Patients who are participating (or who have participated) in qualifying studies and who have not been required to discontinue study treatment for protocol or safety reasons and who have completed required End-of-Treatment and/or Follow-up visits in a prior clinical study with bardoxolone methyl and who, according to the assessment of the investigator, have a potential positive benefit-risk assessment for participating in the trial;
2. Meets the following eligibility criteria based on assessments from the prior qualifying study or from a screening visit, if applicable.
    a. Not expected to reach ESKD or nephrotic syndrome within 12 weeks of study enrollment, in the investigator's judgement; subjects with eGFR < 20 ml/min/1.73m^2 should be discussed with the medical monitor before enrollment (eg, such subjects with an average rate of eGFR decline > 1.0 ml/min/1.73m^2 per month in the 3 months prior to eligibility assessment may not be eligible);
    b. BNP < 200 pg/mL at the last on-treatment visit in the prior qualifying study or at a screening visit, if applicable, as shown in Section 7.1 and Table 5;
    c. No occurrence of a cardiovascular serious adverse event in the prior qualifying study or in the interval between the end of the qualifying study and the screening visit, if applicable.
3. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures;
4. Evidence of a personally signed and dated informed consent document (and assent form if necessary) indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study prior to initiation of any protocol-mandated procedures.

8.2. Patient Exclusion Criteria

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

1. Participation in other investigational clinical studies involving interventional products being tested or used in a way different from the approved form or when used for an unapproved indication;
2. Patients who have an ongoing SAE from a clinical study that is assessed by the investigator as related to bardoxolone methyl;
3. Unwilling to practice acceptable methods of birth control (both males who have partners of childbearing potential and females of childbearing potential) while screening, taking study drug, and 30 days after last study drug dose;
4. Women who are pregnant or breastfeeding;
5. 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;
6. Known hypersensitivity to any component of the study drug.

8.3. Screening Period

The Day 1 visit of EAGLE is not required to be the same day as the End of Study visit of the prior qualifying study. As shown in Table 4, lab assessments from the qualifying study may be used for EAGLE eligibility and maximum treatment dose assignment (Week 100 for CARDINAL or FALCON protocol versions 1.0 through 5.0, and Week 108 [B] for FALCON versions 6.0 and newer) if those assessments were done ≤ 8 weeks before Day 1. In the event the eligibility lab assessments were obtained > 8 weeks before the planned EAGLE Day 1 visit, a screening visit will be required for EAGLE enrollment.

Patients who previously were ineligible due to previous eGFR requirements may be rescreened once.

The maximum bardoxolone methyl dose will be determined by proteinuria status based on the ACR value from the eligibility lab assessments from the prior qualifying study, or for patients requiring a screening visit, the maximum bardoxolone methyl dose will be determined based on the ACR values from the screening labs.

Subjects requiring a screening visit will be consented prior to the start of any screening assessments. All other subjects will be consented at the start of the Day 1 visit, before any procedures are performed for this, or the prior study.

All screening procedures should be completed per the schedule of assessments in Table 5.

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 keeps the same patient number while re-screening procedures are completed. No new patient number is generated, this ensures the patient number during EAGLE will match the one used in the prior qualifying study.

8.4.2. Re-Testing

In rare situations, a specific screening test (eg, 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. Discontinuation

Discontinuation refers to a patient's permanent stopping of administration of study drug and all study assessments and visits for a patient, site, or study. Patients have the right to discontinue study drug and withdraw from the study at any time for any reason, without prejudice to their medical care. Furthermore, the investigator may discontinue a patient from study drug and the sponsor may terminate a specific site or the entire study. Consultation with the medical monitor should occur prior to study drug discontinuation and withdrawing a patient from the study. The reason for a patient's discontinuation from study drug or study termination will be recorded in the electronic case report form (eCRF).

Patients who permanently discontinue from study drug will be asked to complete the End-of-Study procedures noted in Table 5, and withdraw from the trial.

If a patient reaches ESKD (defined as the initiation of maintenance dialysis for 12 weeks or more or kidney transplant), the patient must terminate from the study and should complete an end-of-study visit. The investigator should record the ESKD event as an adverse event and document the date of dialysis initiation or kidney transplantation.

The reason for discontinuation will be recorded in the eCRF. Reasons for discontinuation may include the following. The standardized disposition term is provided, and details are listed in [brackets]:

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

- PROTOCOL-SPECIFIED WITHDRAWAL CRITERIA MET [Reached ESKD (initiation of maintenance dialysis for 12 weeks or more or kidney transplant)];
- STUDY TERMINATED BY SPONSOR [Sponsor termination of the study];
- SITE TERMINATED BY SPONSOR [Premature termination or suspension of an investigational site];
- WITHDRAWAL BY SUBJECT [Administrative reasons (eg, inability to continue); Voluntary withdrawal; Withdrawal of consent];

Patients should temporarily interrupt study drug and the medical monitor should be contacted to discuss if permanent study drug discontinuation is required if any of the following occur. Refer to Section 9.1.2 for additional guidance

- ALT or AST > 8X ULN;
- ALT or AST > 5X ULN for more than 2 weeks;
- ALT or AST > 3X ULN and (total bilirubin > 2X ULN or International Normalized Ratio [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%).

9. TREATMENT OF PATIENTS

9.1. Select Management Guidelines

The following guidelines apply to the management of study participants:

9.1.1. Management of Fluid Status

Specific risk mitigation procedures will be employed to reduce the potential for bardoxolone methyl-induced fluid overload. Laboratory data will be used to monitor fluid status after enrollment. 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. 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.

Additionally, after enrollment and starting study treatment, patients will be closely monitored for rapid weight gain suggestive of fluid overload. Patients will be given a Sponsor-provided scale to use at home to collect and record their weights daily during the first 8 weeks of the treatment period and weekly thereafter. In the event the Sponsor-provided scale is temporarily unavailable (eg, subject is traveling, replacement scale has not arrived to subject, etc.), subjects may use any available scale. Use of a scale other than the Sponsor-provided scale should be documented in the subject diary. During the first 8 weeks, patients who experience a five-pound (2.3 kg) or greater increase in weight in one week or 3 pounds (1.4 kg) in one day should 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 start or increase doses of diuretics (thiazides, loop diuretics) early after recognition of edema. This can be done concurrently with temporary drug interruption and re-initiation. Patients may not restart their study medication until the investigator has completed and documented an assessment of fluid overload.

After Week 8, patients who experience a five-pound (2.3 kg) or greater increase in weight in one week will be instructed to return to the clinic for an unscheduled physical examination and laboratory assessment by the investigator. Study medication should not be interrupted until the investigator has completed and documented an assessment of fluid overload.

Investigators should advise patients to watch for signs and symptoms of fluid overload. Patients should be informed to notify their physicians immediately if they experience swollen feet, chest pain, shortness of breath with mild exertion or while lying down, or other relevant symptoms. The investigator should immediately assess symptoms of fluid overload and determine appropriate medical management, as necessary, including whether stopping drug administration is required. At the earliest sign of worsening or new onset peripheral edema or other signs and symptoms of acute volume overload, investigators will be expected to report if changes to a patient's diuretic regimen have been required to manage edema.

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

For all patients enrolled, nearly all instances of elevated aminotransferases due to bardoxolone methyl treatment are expected to be asymptomatic. Some patients may experience more rapid increases in ALT/AST values than others during the dose titration period. Investigators may consider extending the time between each dose increase to manage ALT/AST elevations.

If a patient's transaminases are elevated, follow the instructions outlined in Table 6.

Table 6: Management of Elevated Aminotransferase Levels (ALT and/or AST)

<table>
<tr><th>ALT and/or AST Level(s)</th><th>Dose Interruption (yes/no)</th><th>Procedure</th></tr>
<tr><td>> 8X ULN</td><td rowspan="4">Yes</td><td rowspan="4">Interrupt 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 (eg, 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 the 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, 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 1 week</td></tr>
<tr><td colspan="3">Abbreviations: 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 restarting study drug after meeting these interruption criteria should start at the 5 mg dose level and dose titrate according to Section 7.3.2.

The hepatobiliary tree must be assessed by ultrasound or magnetic resonance imaging (MRI) for patients who meet temporary interruption criteria. Based on imaging results, if patient additional tests/studies are warranted, this should be discussed with the medical monitor.

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 at the discretion of the investigator, in the management 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

The investigator should evaluate adult patients 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) 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.

The investigator should evaluate adolescent patients for unexplained weight loss of 5% or greater from the Day 1 weight. If 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 to repletion of serum magnesium.

9.1.6. Management of Urinary Protein

Although increases in urinary protein with bardoxolone methyl have not been associated with renal injury or loss of kidney function, investigators should closely monitor patients if urinary albumin to creatinine ratios increase by more than 100% and exceed 1000 mg/g for proteinuria 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 Improving Global Outcomes (KDIGO) Blood Pressure Working Group: ≤ 140 mmHg systolic and ≤ 90 mmHg diastolic for patients with urine ACR < 30 mg/g, and ≤ 130 mmHg systolic and ≤ 80 mmHg diastolic for patients with urine ACR > 30 mg/g (KDIGO, 2012).

Patients being treated with an angiotensin converting enzyme (ACE) inhibitor and/or angiotensin II receptor blocker (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 (eg, hypotension, hyperkalemia), based on the investigator's assessment. Diuretics may be titrated to help maintain blood pressure target levels.

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

9.1.8. Nausea

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

9.1.9. End Stage Kidney Disease

Patients approaching ESKD should be closely monitored by the investigator to fully characterize their progression. For patients with eGFR ≤ 15.0 mL/min/1.73 m^2, initiate more frequent follow-up to closely monitor safety assessments (ie, clinical chemistry (including eGFR), hematology, vital sign assessments (including weight), BNP and N-terminal prohormone B-type natriuretic peptide (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.

Upon initiation of dialysis, study drug should be temporarily 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.

After completing acute dialysis, such patients should continue to undergo frequent follow-up (ie, at least once every 4 weeks [± 2 weeks]) while eGFR ≤ 15.0 mL/min/1.73 m^2. Study drug may be restarted 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. 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 end stage kidney disease should be considered important medical events, and therefore 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 9.9.4 and

Section 9.9.5. Patients should be instructed to inform the site if there is an observed weight loss of more than 3 pounds (1.4 kg) 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 7.

Table 7: 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

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 3.0 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 (eg, infliximab [Remicade®], adalimumab [Humira®], certolizumab pegol [Cimzia®], etanercept [Enbrel®]) within 12 weeks prior to enrollment. 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 or moderate CYP3A4 inhibitors or inducers is prohibited; switching to alternate allowed medication should be considered. If a strong or moderate CYP3A4 inhibitor or inducer is medically necessary, discuss with medical monitor. Subjects who are using these medications prior to screening should have a washout for at least 5-half-lives 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 (eg, infliximab [Remicade®], adalimumab [Humira®], certolizumab pegol [Cimzia®], etanercept [Enbrel®]) is prohibited.

Concomitant use with tolvaptan (patients on tolvaptan who have already enrolled under Version 3 of the protocol may remain in the trial), 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.

Importantly, the administration of any medications listed in this section should be recorded in the concomitant medication page of the electronic data capture (EDC) independent of the patient's study drug status or duration since the patient's last dose of study drug, 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.
- Daily multivitamins or recommended daily supplements;
- Other medications intended to manage concurrent diseases, as authorized by the treating physician;
- Statins (eg, 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.

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. A missed 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

Not applicable

9.6. 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;

Any operational need that would require the patient to return to the site between scheduled visits.

9.7. Pregnancy

9.7.1. 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 (eg, 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 9.7.2.

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).

Pregnancy using frozen embryos of subject or subject partner is not permitted in the study.

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).

9.7.2. 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 (eg, 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 (if necessary) or day 1 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 following administration of the final dose of study medication, fertile males who have female partners of childbearing potential must practice one of the following acceptable methods of birth control:

- Have had a vasectomy (performed at least 6 months prior to screening (if necessary) or day 1 with the appropriate post-procedure documentation of surgical success);
- Use double barrier contraception method, defined as male use of a condom and female use of a barrier method (eg, 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 (eg, 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.

9.7.3. Suspected Pregnancy

During the study, all WOCBP must be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, 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 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 discontinue taking study drug. A patient must also discontinue study drug if their partner becomes pregnant. 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.

9.8. Serious Toxicities

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

9.9. Study Procedures

The following sections describe each assessment. The timing of these assessments is noted in Table 5. All Day 1 procedures, except AE assessments, should be completed prior to administration of first dose of study drug.

9.9.1. 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.

9.9.2. Inclusion/Exclusion

Inclusion and exclusion criteria must be reviewed as indicated in Section 8. Patients must meet all 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 enrolling the patient on Day 1.

9.9.3. 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 (ie, medications that the patient is taking or has taken within 30 days prior to Day 1) will be reviewed as indicated in Table 5 and all changes will be recorded.

9.9.4. Height

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

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.

9.9.5. Weight and Body Mass Index (BMI)

Weight must be measured as indicated in Table 5. BMI will be calculated in the eCRF each time the weight is recorded. The Sponsor will provide each patient with a scale to use at home to measure weight, and a diary will be provided to record the at-home weight measurements. Weights recorded in patient diaries will not be entered in the eCRF. Weights should be taken at approximately the same time each day and recorded in a patient diary. During the first eight weeks, weights will be recorded daily; weekly weights will be recorded thereafter. Patients will be instructed to stop administering study drug and contact the investigator if their daily weight increases 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.

9.9.6. Vital Sign Measurements

Vital sign measurements include the patient's heart rate (beats/minute taken for at least 15 seconds), respiration rate, blood pressure, and body temperature. Blood pressure should be taken after the patient has rested in a sitting position for at least 5 minutes. The same arm

(usually the non-dominant arm) and the appropriate size cuff should be used for each measurement. Vital sign measurements should be taken as indicated in Table 5 .

9.9.7. Physical Examination

A physical examination must be performed by a physician, physician assistant, or registered nurse practitioner as indicated in Table 5 and as documented within the table footnotes. A complete physical examination is required at Day 1, Week 1, Week 2, Week 4, Week 6, Week 8, Week 12, Week 24, every 24 weeks thereafter, and at the end of study, and must include the following organ or body system assessments: head, eyes, ears, nose, throat, musculoskeletal, cardiovascular, lymphatic, respiratory, abdomen, skin, extremities, and neurological. Clinically significant findings at Day 1 must be recorded as medical history if there was a time delay between this study and the prior qualifying study and this finding was not captured in the previous study. Following the examination on Day 1, new or changed physical examination findings meeting the criteria for an adverse event must be recorded as an adverse event. The investigator or his/her appointed designee is primarily responsible to perform the physical exam. If the appointed designee is to perform the physical exam, he/she must be permitted by local regulations and his/her name must be included on any globally and locally required documents (eg, individual must be added for all sites on a United States (US) Food and Drug Administration [FDA] Form 1572). Whenever possible, the same individual should perform all physical exams.

9.9.8. Pregnancy Test

WOCBP (see Section 9.7) will complete a pregnancy test as indicated in Table 5, or at any time if pregnancy is suspected. Negative test results are required on Day 1 before study drug administration. Any patient who becomes pregnant during the study must discontinue taking study drug immediately. See Section 9.7.3 for a description of procedures to be followed in case of pregnancy.

9.9.9. Study Drug Administration

Patients should self-administer one dose orally as indicated in Section 7.3.1 . 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.

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

9.9.10. Study Drug Dispensation and Collection

Study drug will be dispensed and collected from the patient as indicated in Table 5. 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, and every 24 weeks thereafter for the duration of the study. 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 (eg, a 3-month supply) cannot be dispensed as outlined in Table 5, 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.

9.9.11. Telephone Contact

Patients will be contacted by telephone as indicated in Table 5. Patients will be asked about their body weight and other signs of fluid retention, as well as AEs and any changes to concomitant medications. If fluid retention is suspected, the patient 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.

9.9.12. Adverse Event Collection

Patients will be observed for general appearance, presence of illness or injury, or signs indicative of a concurrent illness as indicated in Table 5. Patients must be instructed to volunteer any information regarding AEs on or after the first dose of study drug or sites may query the patients with an open question regarding any AEs they may be experiencing (eg, "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).

See Section 11 for more detail regarding adverse events.

9.9.13. Clinical Chemistry

Samples will be collected for clinical chemistry analyses as indicated in Table 5. These include albumin, alkaline phosphatase, ALT, AST, bicarbonate, bilirubin direct, bilirubin total, BUN/urea, calcium, chloride, creatine kinase (CK), creatinine, eGFR, ferritin, GGT, glucose, LDH, magnesium, phosphorus, potassium, protein total, sodium, and uric acid.

9.9.14. Hematology

Complete blood count (CBC) collection will be performed following the visit schedule indicated in Table 5. The CBCs will be offered optionally on the unscheduled visits. The tests include: hematology; anisocytosis, basophils, basophils absolute, eosinophils, eosinophils absolute, hematocrit, haemoglobin, hypochromasia, lymphocytes, lymphocytes absolute, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), microcytosis, monocytes, monocytes absolute, neutrophils, neutrophils absolute, platelet count, red blood cell (RBC) count, teardrop cells, and white blood cell (WBC) count.

9.9.15. eGFR

The eGFR value will not be calculated by the central lab. 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/assent in the original, qualifying study. For patients consented at age 18 years and older, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation will be used:

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

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

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

Where 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 serum creatinine lab collection.

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.

9.9.16. N-Terminal Prohormone B-type Natriuretic Peptide (NT-proBNP) and Brain Natriuretic Peptide (BNP)

Samples will be collected for NT-proBNP and BNP as indicated in Table 5. As recent exercise may affect BNP and NT-proBNP levels, patients should be allowed to rest for approximately 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, eg, sitting or semi-recumbent.

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

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

Albumin/creatinine ratio will be measured by first morning void spot urine collection as indicated in Table 5. Appropriate containers for the collection will be provided to the patient at the visit prior to the collection.

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

9.9.18. Lipid Panel

Samples will be collected for the following lipid assessments as indicated in Table 5: 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.

9.9.19. Medical History

If the patient delays their study enrollment from the last day of the prior qualifying study, they should complete an entry into the Medical History eCRF to capture any events that occurred during the time period between the studies.

9.9.20. Tanner Staging

Gender appropriate Tanner staging will be performed on all ADPKD patients if the patient enrolls in the study as an adolescent. Tanner staging should be performed as outlined in Table 5, 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).

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.

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 high-density polyethylene (HDPE) bottles. Each bottle will utilize foil induction-seal liners and a child-resistant closure. Each bottle of study drug will contain 30 or 90 capsules of 5 mg, 10 mg, 15 mg, or 20 mg strength bardoxolone methyl. 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-1803;
- 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 IP for use and distribution in the European Union (EU) shall adhere to current Eudralex, Volume 4 Annex 13 guidance and requirements.

In the event the IP is not packaged as intended or may not adhere to current good manufacturing practices (cGMP), a complaint should be filed with the Sponsor. 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° to 25°C (59° to 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 IP.

10.4. Study Drug Administration

Please refer to Section 9.9.9 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 5. Patients must be instructed to continue taking study drug once daily 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, 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 or not 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 End of Study Visit as indicated in Table 5) 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 or through the End of Study Visit, whichever is earlier. In addition, as noted in Section 11.2.1.2, death, kidney disease, or initiation of transplant should be reported as SAEs through the End of Study visit.

AEs that are related to study procedures should be reported independent of the patient's study 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 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.

Initiation of dialysis (acute and/or maintenance) and receipt of kidney transplant due end stage kidney disease, as defined Section 9.1.9, should be considered important medical events.

Pregnancy is not considered an AE; however, information will be collected for any pregnancies that occur during the study (from the time of the first dose of study drug until the final visit indicated in Table 5, as appropriate). Certain pregnancy outcomes will require submission as an SAE (see Section 9.7).

The investigator is responsible for reporting to Reata or designee all AEs and SAEs that are observed or reported by the patient during the study (from the time of administration of the first dose of study drug until the final visit indicated in Table 5, 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. 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, should be reported through the End of Study visit 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.

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

11.3. Eliciting Adverse Event Information

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

In addition to patient observations, AEs must be documented for any clinically significant diagnosis resulting from abnormal laboratory test values, physical examination findings, or 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 (eg, 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 adverse events in the prior trial with bardoxolone methyl. Any new event/condition that starts during the gap between prior qualifying study and Day 1 of EAGLE should be recorded as medical history in EAGLE. 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.

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 (eg, 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 results will be followed through the 30 days after the last dose of study drug.

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 (eg, "worsening of…"). Any improvement in condition should be documented per Section 9.9.7.

Each AE should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory test values) 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 are only considered AEs if they are judged to be clinically significant (ie, 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 are the result of pathology for which there is an overall diagnosis (eg, 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 (eg, elective periodontal surgery). However, if a pre-planned procedure is performed early (eg, 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/email the completed SAE form [redacted] within 24 hours of awareness.

[redacted]

[redacted] Facsimile: [redacted] or [redacted]

E-mail: [redacted]

For questions regarding SAE reporting, contact your study manager, medical monitor, or [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 (eg, subject discharge summary or autopsy reports), should be faxed or emailed to [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 IRB or IEC, as appropriate.

Principal investigators are responsible for informing their IRB/IEC of any SAEs at their site. SAE correspondence with regulatory authorities or IRBs/IECs 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

The aim of this long-term extended access study is primarily to provide continuing bardoxolone methyl treatment to patients and to assess long term safety and tolerability, hence no single primary variable has been identified. Patient numbers will be determined by those who are participating (or who have previously participated) in a qualifying clinical study with bardoxolone methyl.

12.2. Study Variables

12.2.1. Safety Variables

The safety variables include results of physical examinations, laboratory test results, ACR, vital sign measurements, height, weight, AEs, and SAEs.

12.3. Statistical Analyses

A statistical analysis plan (SAP) detailing the analyses will be developed prior to database lock. All statistical analyses and data summaries will be performed using SAS® (Version 9.3 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. Primary Analysis of Safety

As the extension is an open-label design with no comparator group, all statistical analyses will be descriptive.

The summary tables will be presented for the overall group of patients, and also split by previous treatment groups (ie, bardoxolone methyl or placebo) in prior bardoxolone methyl clinical studies.

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/IEC review, and regulatory inspections, by providing direct access to all study records. In the event of an audit, the principal investigator agrees to allow the Sponsor, representatives of the Sponsor, the US FDA, and other relevant regulatory authorities access to all study records.

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

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1. Quality Assurance

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

14.2. Financial Disclosure

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

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

14.3. Sponsor Obligations

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

14.4. Investigator Documentation

Before beginning the study, the principal investigator will be asked to comply with ICH E6(R2) 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/IEC approval of the protocol;
- The IRB- or IEC-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 Independent Ethics Committee (IEC) Review

The protocol and the proposed informed consent form (and assent if applicable) must be reviewed and approved by a properly constituted IRB/IEC 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/IEC 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/IEC chairperson or designee must sign all IRB/IEC approvals and must identify the IRB/IEC 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/IEC, 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 (eg, US Code of Federal Regulations Title 21, European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

The principal investigator agrees to conduct the study in accordance with the ICH Guidance for Industry on GCP ICH E6(R2)] 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 (or assent form if necessary), 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/IEC submission. Once reviewed, the consent will be submitted by the principal investigator to his or her IRB/IEC 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 (or assent as required) to participate in the study by signing the informed consent form (or assent form, if necessary).

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent. Informed consent and assent, if necessary, must be obtained before conducting any study-specific procedures (ie, all of the procedures described in the protocol). The process of obtaining informed consent (and assent, if necessary) 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/IEC, and a copy of the approved version and the notice of approval must be provided to the Sponsor's designated monitor after IRB/IEC approval.

In person (in-clinic) informed consenting must be performed during the initial screening or enrollment visits. All other informed consenting will be allowed to be performed remotely, if permitted by your local regulations. The principal investigator or designee will provide a copy of the informed consent form and/or assent form as necessary (signed copy to be provided per applicable law) to the patient and/or legal guardian. 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/IEC.

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/IEC, 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/IEC.

The investigator is responsible for informing the IRB/IEC 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/IEC 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/IEC approval. The Sponsor and IRB/IEC 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 1 Section 4. 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 Appendix 1 Section 4, 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 EDC system will be used to capture data electronically for all patients enrolled in the study.

17. PUBLICATION POLICY

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

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

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19. APPENDICES

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 AND 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 interrupted. The sponsor must be notified immediately for additional guidance.

Study dug 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 (eg, loss of taste or smell), the patient should be encouraged to repeat SARS-CoV-2 testing 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 (ie, appropriate dose for restarting and appropriate visit schedule) are contained in Section 7.3.3.

3. STUDY DRUG ACCESS

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. patient

4. STUDY VISITS

If sites foresee upcoming closures or other issues impacting the patient's ability to come in for frequent visits (first 8 weeks), consider postponing the patient's enrollment. The Day 1 visit of EAGLE will not be required to occur on the same day as the end-of-study visit of prior qualifying study.

For continued patient safety oversight, patients should continue with protocol-specified visits. Where inadvisable for the patient to be seen for an in-person, in- clinic visit or if a patient is unwillingly 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
  - Urine collection for ACR
  - Urine pregnancy test for WOCBP
- Vital signs
- Weight at home
- Adverse event assessment

- Prior and concomitant medication assessment

5. DOSE MANAGEMENT

5.1. Dose De-escalation and Interruption for Missed Safety and Laboratory Assessments

If no scheduled in -clinic visit is completed and remote assessments/laboratory samples cannot be collected within the 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, that 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 interrupted until safety lab values can be evaluated and it is deemed appropriate to restart. Appendix 1 Section 5.2 describes the procedure for resuming and dose-escalating IP following drug interruption.

5.2. Resuming or Dose-escalating IP after Interruptions or Changes

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 that 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 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 (eg, 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**
IP temporarily interrupted for any reason (eg, 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 (eg, 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 in-clinic 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 9.6 of the protocol. Once the target dose has been reached and 2-week follow-up completed, the Schedule of Assessments may be resumed.

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.

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. A CRF form has been updated to collect data for COVID-19 impact. Adjusting monitoring activities may include a combination of on-site and off-site monitoring. Remote source data verification may also be taken into consideration.

AMENDMENT CHANGE DOCUMENT
CLINICAL STUDY PROTOCOL 402-C-1803
Study Title: AN EXTENDED ACCESS PROGRAM TO ASSESS LONG TERM SAFETY OF BARDOXOLONE METHYL IN PATIENTS WITH CHRONIC KIDNEY DISEASE (EAGLE)

Protocol History

Version 01	04 September 2018
Version 02	31 January 2019
Version 03	30 June 2020

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] E-mail: [redacted] [redacted] ~~E-mail:~~ [redacted]	Updated contact information for SAE Reporting
Section 4 List of Abbreviations and Definitions of Terms	Added/corrected multiple acronyms	Updated terms
Section 5.1 Clinical Experience with Bardoxolone Methyl	~~Approximately, 2090~~Overall, bardoxolone methyl has been tested in multiple CKD studies and over 3000 individuals have been exposed to bardoxolone methyl.	Updated number of subjects exposed

Section	Version 3							Rationale
Section 5.1.1 Efficacy (Table 3)	RTA402-005 (TSUBAKI)	2/ Japan	Randomized, Double-Blinded, Placebo-Controlled	Age >=20, T2D and Stage 3 and 4 CKD	~~108~~1 20	16 weeks	6.6 (inulin GFR) (p=0.008 vs PBO)	Updated data for the Cross-Study Comparison of Increases in eGFR, Inulin Clearance, and Creatinine Clearance with Bardoxolone Methyl Treatment
	402-C-1603	2/US	Multicenter, Open-label,	Age 12 to 65, Alport syndrome	30	48 weeks	10.4 (p<0.001)	
	402-C-1603 Year 1	3/Global	Randomized, Double-Blinded, Placebo-Controlled	Age 12 to 70, Alport Syndrome	157	48 weeks	9.5 (p<0.001 vs PBO)	
	402-C-1702	2/US	Multicenter, Open-label	Age ≥ 18, ADPKD	31	12 weeks	9.3 (p<0.001)	
	402-C-1702	2/US	Multicenter, Open-label	Age 18 to 70, IgA Nephropathy	26	12 weeks	8.0 (p<0.0001)	
	402-C-1702	2/US	Multicenter, Open-label	Age 18 to 70, T1D CKD	28	12 weeks	5.5 (p=0.025)	
	402-C-1702	2/US	Multicenter, Open-label	FSGS	18	12 weeks	7.8 (p=0.003)	
Section 7.1 Overall Study Design	The CARDINAL study (402-C-1603, NCT03019185, EudraCT 2016-004395-22) and FALCON (402-C-1808, NCT03918447, EudraCT 2018-004651-20 are ~~is~~ the only qualifying clinical studies~~y~~ at this time							Added FALCON as another qualifying study to enroll in EAGLE

Section	Version 3	Rationale
Section 7.1 Overall Study Design	The Day 1 visit of EAGLE will not be required to occur on the same day as the last visit of the prior qualifying study (e.g. Week 104 in CARDINAL). The last on-treatment lab assessments (Week 100) should be used for patient eligibility, unless the last on-treatment lab assessments are more than approximately 8 weeks old and the end-of-study lab assessments ~~Week 104 labs~~ are more than 4 weeks old relative to Day 1 of EAGLE. In this case, a screening visit is required to enroll in EAGLE study and begin study drug treatment. Table 4 below clarifies potential situations with patient eligibility. The maximum bardoxolone methyl dose will be determined by proteinuria status based on the ACR value from the last on-treatment visit in the prior qualifying study or for patients requiring a screening visit, maximum bardoxolone methyl dose will be determined based on the ACR values from screening labs. ~~Day 1 for this extended access study should occur on the same day as the last visit in the prior qualifying clinical study.~~ If the Day 1 visit for EAGLE is the same as the end-of-study visit from the prior qualifying study, the ~~Assessments~~ assessments required for both ~~the last~~ visits ~~in the prior qualifying study and Day 1 for this study~~ should only be completed once. If the Day 1 visit of EAGLE is not on the same day as the end-of-study visit from prior qualifying study, lab assessments will be performed for Day 1 through the EAGLE central lab. Table 4 has been added to reflect the changes to lab assessments for eligibility.	Clarification for lab assessments to use for patient eligibility and ACR value in determining maximum drug dose
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 3 of the Protocol, modifications intended to address access to and administration of investigational product, 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 7.2 Number of Patients	Patient numbers will be determined by those who ~~have been treatment compliant~~are participating and who have previously participated in a ~~prior~~ qualifying clinical study with bardoxolone methyl.	

Section	Version 3	Rationale
Section 7.3.1 Dose Escalation	Dose escalation may proceed slowly if the patient experiences early elevation in ALT/AST over ULN e.g. at Week 2 (See Section 9.1.2). The investigator should discuss any reason for not dose-escalating at Weeks 2, 4, or 6 with the medical monitor.	Updated dose escalation description
Section 7.7 Schedule of Assessments	Revised the Schedule of Assessments (Table 5) to reflect additional screening visits, hematology assessment, and updated footnotes.	Updated Table 5 to reflect changes/updates in screening, added hematology assessment, and updated footnotes

Section	Version 3	Rationale
Section 8.1 Patient Inclusion Criteria	1. ~~Treatment compliant~~ Patients who are participating (or who have participated) in qualifying ~~ongoing~~ studies and who have not been required to discontinue study treatment for protocol or safety reasons and who have completed required End-of-Treatment and/or Follow-up visits in a prior clinical study with bardoxolone methyl and who, according to the assessment of the investigator, have a potential positive benefit-risk assessment for participating in the trial; 2. Meets the following eligibility criteria based on assessments from the prior qualifying study (last on-treatment visit) or from a screening visit if applicable. a. Not expected to reach end stage kidney disease (ESKD) or nephrotic syndrome within 12 weeks of study enrollment, in the investigator's judgement; subjects with eGFR <20 ml/min/1.73m^2 should be discussed with the medical monitor before enrollment (e.g., such subjects with an average rate of eGFR decline > 1.0 ml/min/1.73m^2 per month in the 3 months prior to eligibility assessment may not be eligible) ~~a. eGFR ≥ 30 mL/min/1.73m^2 at the last on-treatment visit in the prior qualifying study;~~ b. BNP < 200 pg/mL at the last on-treatment visit in the prior qualifying study or at a screening visit, if applicable, as shown in Section 7.1 and Table 4 c. No occurrence of a cardiovascular serious adverse event in the prior qualifying study or in the interval between the end of the qualifying study and the screening visit, if applicable.	Updated inclusion criterion number 1 and 2
Section 8.2 Patient Exclusion Criteria	3. Unwilling to practice acceptable methods of birth control (both males who have partners of childbearing potential and females of childbearing potential) while screening, taking study drug and 30 days after last study drug dose;	Updated exclusion criteria number 3 about birth control
Section 8.3 Screening and Re-screening Period	**Screening and Re-screening** A screening visit is required for subjects if the last on-treatment lab assessments (Week 100) are more than approximately 8 weeks old and the end-of-study assessments (Week 104) are more than 4 weeks old from relative to Day 1 of EAGLE. Subjects who previously were ineligible due to previous eGFR requirements may be rescreened once.	Added new section 8.3 to clarify screening and re-screening

Section	Version 3	Rationale
Section 8.4	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. Refer to Section 9.1.2 for additional guidance.	Updated to refer section 9.1.2 for more information
Section 9.11 Management of Fluid Status	Specific risk mitigation procedures will be employed to reduce the potential for bardoxolone methyl-induced fluid overload. Laboratory data will be used to monitor fluid status after ~~randomization~~ enrollment Additionally, after ~~randomization~~ enrollment and resuming study treatment, patients will be closely monitored for rapid weight gain suggestive of fluid overload.	Clarification
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. Dose escalation may proceed more slowly if the patient experiences early elevation in ALT/AST over ULN e.g. at Week 2. Medical monitor may be consulted for additional guidance.	Updated section to manage ALT/AST elevations
Section 9.1.2 Management of Elevated Transaminase Levels (ALT and/or AST)	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.	Updated information for resuming drug therapy after temporary discontinuation due to elevated liver enzymes
Section 9.1.3. Management of Muscle Spasms	Assessment of levels of electrolytes such as magnesium, calcium, and potassium may indicate the need for replacement. Serum vitamin D levels may be collected at the discretion of the investigator, in the management of muscle spasms. If vitamin D levels are low, supplementation may be warranted. Muscle relaxants may also help relieve symptoms.	Updated section for serum vitamin-D measurements

Section	Version 3	Rationale
Section 9.1.7 Management of Blood Pressure	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.	Updated text

Section	Version 3	Rationale
Section 9.1.9 End Stage Kidney Disease	**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 at least once every 4 weeks (± 2 weeks), 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. After completing acute dialysis, 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. See Section 8.4 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 therefore recorded as SAEs.	Added new section regarding ESKD

Section	Version 3	Rationale
Section 9.2 Description of Study Drug	Table 6 has been updated to reflect additional bardoxolone methyl capsules strengths.	Updated to reflect new IP kit configuration/ dose strengths
Section 9.3.1 Excluded Medications	**Excluded Medications** The following medications/medication classes are not permitted during the study • Any other investigational drug • Chronic (> 2 weeks) immunosuppressive therapy, or need for corticosteroids, including therapies such as glucocorticoids, oncologic preparations, and anti-TNFα agents [e.g., infliximab (Remicade®), adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®)]. (Glucocorticoid intra-articular injections, inhaled products, topical preparations, and nasal preparations are allowed.) Patients who take excluded medications during the study should not discontinue study drug solely on this basis. Consultation with the medical monitor should occur prior to study drug discontinuation or withdrawing a patient from the study	Added excluded medications subsection to Concomitant Medications
Section 9.6 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 diary. Additional conversations may be necessary with the medical monitor following an unscheduled visit to assess patient safety.	Added hematology assessment to unscheduled visits

Section	Version 3	Rationale
Section 9.7.1 Women of Childbearing Potential and Fertile Males	Section 9.7.1 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 orchidectomy or vasectomy at least 6 months earlier with the appropriate post-procedure documentation of surgical success).	Updated text regarding birth control for WOCBP and Fertile Males

Section	Version 3	Rationale
Section 9.7.2 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: • Vasectomized partner (with vasectomy performed at least 6 months prior to screening or day 1 with the appropriate post-procedure documentation of surgical success); partner *must* be the sole partner for that patient. 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: • Partner contraception methods; *must* be the sole partner for that patient – ~~Partner~~ Use of an intrauterine device; – ~~Partner~~ 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;	Updated text about Method of Birth Control
Section 9.9.3 Prior and Current Concomitant Medications	~~Concomitant~~ Prior and concomitant medications (medications that the patient is taking or has taken within 30 days prior to Day 1) will be reviewed as indicated in Table 5 and all changes will be recorded	Updated text for clarification

Section	Version 3	Rationale
Section 9.9.7 Physical Examination	A complete physical examination is required at Day 1, Week 1, Week 2, Week 4, Week 6, Week 8, Week 12, Week 24, every 24 weeks thereafter, and at the end of study, and must include the following organ or body system assessments: head, eyes, ears, nose, throat, musculoskeletal, cardiovascular, lymphatic, respiratory, abdomen, skin, extremities, and neurological.	Added missing assessments timepoints
Section 9.9.9 Study Drug Administration	Patients under the age of 18 should self-administer ~~one~~ recommended dose orally every other day for the first week, and begin dosing once a day on Day 7 through the end of the study, as indicated in Section 7.3.1.	Clarification
Section 9.9.10 Study Drug Dispensation and Collection	The patient will be dispensed 1 or more treatment kits at Day 1, Week 2, Week 4, Week 6, Week 8, Week 12, Week 24, and every 24 weeks thereafter for the duration of the study.	Added missing timepoint of drug dispensation
Section 9.9.13 Clinical Chemistry	Samples will be collected for clinical chemistry analyses as indicated in Table 5. These include Albumin, Alkaline Phosphatase, ALT, AST, Bicarbonate, Bilirubin Direct, Bilirubin Total, BUN/Urea, Calcium, Chloride, CK, Creatinine, eGFR, Ferritin, GGT, Glucose, LDH, Magnesium, Phosphorus, Potassium, Protein Total, Sodium, and Uric acid.	Updated text
Section 9.9.14 Hematology	**Hematology** CBC collection will be performed following the visit schedule indicated in Table 5. The CBCs will be offered optionally on the unscheduled visits. The tests include: Hematology; Anisocytosis, Basophils, Basophils Absolute, Eosinophils, Eosinophils Absolute, Hematocrit, Haemoglob in, Hypochromasia, Lymphocytes, Lymphocytes Absolute, MCH, MCHC, MCV, Microcytosis, Monocytes, Monocytes Absolute, Neutrophils, Neutrophils Absolute, Platelet count, RBC, Teardrop Cells, and WBC.	Added a section for Hematology
Section 9.9.15 eGFR	The eGFR value will not be calculated by the central lab. 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 in the original, qualifying study.	Clarification on the calculation of the eGFR value by central lab

Section	Version 3	Rationale
Section 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 results of physical examinations, vital sign measurements, AEs, SAEs, weight, UACR, and laboratory test results.	Updated text to include results of physical examinations as safety parameters
Section 11.2.1.2 Serious Adverse Events	• Patient reaches ESKD (defined as the initiation of maintenance dialysis for 12 weeks or more or kidney transplant)	Updated section with a new bullet point for consistency
Section 11.6 Recording Adverse Events	Any new event/condition that starts during the gap between prior qualifying study and Day 1 of EAGLE should be recorded as medical history in Eagle. After the first dose, documentation of AEs (ongoing and with start date after Day 1) shall continue until 30 days (+/- 3 days) following administration of the final dose of study medication, regardless of the relationship of the AE to study drug. … All other AEs will be followed through 30 days after the final visit indicated in Table 5, as appropriate	Updated for clarification regarding recording of AEs between prior qualifying study and Day 1 of EAGLE

Section	Version 3	Rationale
Section 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/email the completed SAE form to [redacted] (fax numbers listed in Table 7~~Table~~) within 24 hours of awareness. [redacted] [redacted] ~~Telephone:~~ [redacted] ~~Facsimile:~~ [redacted] E-mail: [redacted] [redacted] ~~Telephone:~~ [redacted] ~~Facsimile:~~ [redacted] **For questions regarding SAE reporting, contact your study manager, medical monitor, or** [redacted] Within 24 hours of receipt of new information, the updated follow-up SAE form, along with any supporting documentation (*e.g.*, subject discharge summary or autopsy reports), should be faxed to [redacted]	Updated SAE reporting vendor

Section	Version 3	Rationale
Section 12.1 Sample Size	Patient numbers will be determined by those who ~~have been treatment compliant~~are participating and ~~who~~ have previously participated in a qualifying clinical study~~ies~~ with bardoxolone methyl.	Updated text for qualifying clinical study
Section 12.2.1	The safety variables include results of physical examinations, results of laboratory test results, UACR, vital sign measurements, weight, AEs, and SAEs.	Updated text to include results of physical examinations
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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ~~Internation Conference on Harmonization~~ (ICH) guideline E6(~~R1~~R2): Good Clinical Practice: Consolidated Guideline and current standard operating procedures.	Updated to newer guidelines version
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 to newer guidelines version

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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ~~Internation Conference on Harmonization~~ (ICH) for Guidance for Industry on Good Clinical Practice (GCP) ICH E6(~~R1~~R2) 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/ ~~http://www.wma.net/en/30publications/10policies/b3/~~]The principal investigator must conduct all aspects of this study in accordance with all national, state, and local laws or regulations.	Updated ICH guidelines and Declaration of Helsinki links
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 (R~~1~~2), and principles of the Declaration of Helsinki	Updated to newer guidelines
Section 19 Appendices	Appendix 1 (COVID-19 Mitigations) was added	COVID-19 Mitigation Appendix was added to describe protocol modifications due to the pandemic

AMENDMENT CHANGE DOCUMENT
CLINICAL STUDY PROTOCOL 402-C-1803
Study Title: AN EXTENDED ACCESS PROGRAM TO ASSESS LONG TERM SAFETY OF BARDOXOLONE METHYL IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Protocol History

Version 01	04 September 2018
Version 02	31 January 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
Section 7.1 Overall Study Design	This extended access study will assess the long-term safety and tolerability of bardoxolone methyl in qualified patients with chronic kidney disease (CKD) who previously participated in ~~one of the~~ a qualifying clinical ~~studies~~ study with bardoxolone methyl. The CARDINAL study (402-C-1603, NCT03019185, EudraCT 2016-004395-22) is the only qualifying clinical study at this time.	Defined qualifying clinical study
Section 7.2 Number of Patients	Patient numbers will be determined by those who have been treatment-compliant and who have previously participated in ~~one of the~~ a prior qualifying clinical ~~studies~~ study with bardoxolone methyl.	Clarification
Section 7.7 Schedule of Assessments	BNP and~~/or~~ NT-Pro BNP	Clarification based on intent to measure BNP and NT-Pro BNP levels