FDA Briefing Document

NDA# 215484

Drug name: Bardoxolone Methyl

Applicant: Reata Pharmaceuticals, Inc.

Cardiovascular and Renal Drugs Advisory Committee Meeting

[12/08/21]

Division of Cardiology and Nephrology/ Office of Cardiology, Hematology, Endocrinology and Nephrology

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GLOSSARY

ABPM	Ambulatory Blood Pressure Monitoring
AC	Advisory Committee
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AS	Alport syndrome
AST	aspartate aminotransferase
BNP	B-type natriuretic peptide
BP	blood pressure
C_{avg}	average concentration
CKD	chronic kidney disease
COVID-19	coronavirus disease 2019
DBP	diastolic blood pressure
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
ETA	distribution of η
FDA	Food and Drug Administration
IIV	inter-individual variability
I_{max}	maximal effect of inhibition
ITT	intention-to-treat
Keap1	Kelch-like ECH-associated protein 1
K_{in}	apparent increase rate constant
K_{out}	first order elimination rate constant
K_{prog}	rate of disease progression
LS	least squares
Nrf2	nuclear factor erythroid 2–related factor 2
NT-proBNP	N-terminal proB-type natriuretic peptide
OFV	objective function value
PD	pharmacodynamic
PK	pharmacokinetic
PopPK	population pharmacokinetics

QD	once daily
RSE	relative standard error
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC_{50}	half-maximal stimulatory concentration
SD	standard deviation
S_{max}	maximal effect of stimulation
T2D	type 2 diabetes
UACR	urinary albumin-to-creatinine ratio

1. EXECUTIVE SUMMARY/DRAFT POINTS FOR CONSIDERATION BY THE ADVISORY COMMITTEE

1.1. Purpose/Objective of the AC Meeting

The Food and Drug Administration (FDA) is convening this Advisory Committee (AC) meeting to discuss whether the results of the CARDINAL Phase 3 study demonstrate that bardoxolone (proposed trade name IMBARKYD) slows the loss of kidney function in patients with Alport Syndrome (AS) and whether it is reasonable to conclude, based on the available data, that bardoxolone, when used chronically, will reduce the risk of progression to kidney failure in patients with this disease.

1.2. Context for Issues to Be Discussed at the AC Meeting

Alport syndrome is a rare genetic disease caused by mutations in genes encoding the alpha-3, alpha-4, and/or alpha-5 chains of type IV collagen found in the basement membranes of kidney glomeruli, cochleae, and eyes. The impaired production of alpha chains leads to disruption of the collagen matrix and abnormal basement membrane structure and function, leading to progressive loss of kidney function and kidney failure, sensorineural deafness, and ocular abnormalities, which lead to loss of vision in some patients. There are no approved treatments for AS, and there is urgent need for therapies that can reduce the risk of progression to kidney failure.

Kidney failure is associated with significant morbidity and mortality; however, it is also a late outcome of chronic kidney disease (CKD). We therefore use a surrogate endpoint to assess whether a drug is effective in reducing the risk of progression to kidney failure (i.e., changes in estimated glomerular filtration rate [eGFR] that are indicative of a progressive irreversible loss of kidney function) and as a basis for full approval of drugs intended to treat CKD. For example, in 2018, the FDA approved a drug to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease based on evidence that the drug slowed the loss of kidney function in earlier and later stages of disease and that the benefit accrued over time (1 to 3 years). Based on such data, the FDA concluded that the drug, when used chronically, would have a meaningful impact on the risk of progression to kidney failure (Food and Drug Administration 2018; Otsuka Pharmaceutical 2018).

Drugs can also have reversible pharmacodynamic (PD) effects on kidney function measured by eGFR (i.e., drugs can cause reversible increases or decreases in eGFR). These are of unclear clinical significance, but they complicate the ascertainment of the effect of a treatment on chronic progression of disease. In the case being discussed, the reversible effect is an increase in eGFR which appears to take several months to manifest fully.

1.3. Brief Description of Issues for Discussion at the AC

On February 25, 2021, Reata Pharmaceuticals, Inc. (Applicant) submitted a New Drug Application for bardoxolone, a nuclear factor erythroid 2–related factor 2 (Nrf2) activator, to slow the progression of kidney disease in patients 12 years of age and older with CKD caused by AS. In support of the proposed indication, the Applicant submitted the results of the CARDINAL study. CARDINAL was an international, multicenter, phase 2/3 study that evaluated the safety, tolerability, and efficacy of bardoxolone in patients with AS. The study included two cohorts: an open label, single-arm, phase 2 cohort that

enrolled 30 patients in the US (CARDINAL Phase 2) and a subsequent double-blind, randomized, placebo-controlled, phase 3 cohort (CARDINAL Phase 3) that enrolled 157 patients globally.

The primary and key secondary study endpoints in CARDINAL Phase 3 were as follows:

- Primary: Change from baseline in eGFR at Week 48 (Year 1) and Week 100 (Year 2)
- Secondary: Change from baseline in eGFR, following a 4-week drug treatment withdrawal period, at Week 52 (Year 1) and Week 104 (Year 2)

The FDA review team agrees that CARDINAL Phase 3 met its prespecified primary and key secondary endpoints, endpoints that assessed on-treatment and off-treatment changes in kidney function (i.e., eGFR), respectively. Nevertheless, we are bringing this application to an AC because we believe the findings in the study warrant public discussion. Specifically, we are seeking input from the AC on:

- Whether the observed effects on kidney function are indicative of an effect on disease progression in patients with AS (i.e., that bardoxolone slows the loss of kidney function or has any effect beyond a reversible, PD effect on kidney function)
- Whether it is reasonable to conclude, based on the available data, that bardoxolone, when used chronically, will reduce the risk of progression to kidney failure in patients with AS

1.4. Draft Points for Consideration

The Applicant is seeking approval of bardoxolone to slow the progression of kidney disease in patients 12 years of age and older with CKD caused by AS. Discuss the following:

- Whether CARDINAL Phase 3 was adequately designed to assess for bardoxolone's effect on progression of kidney disease
- Whether the available data indicate that bardoxolone slows the progression of kidney disease and whether it is reasonable to conclude, based on the available data, that bardoxolone will reduce the risk of progression to kidney failure when used chronically in patients with AS
- Whether bardoxolone's effects on albuminuria and blood pressure raise concern for long-term safety and/or efficacy

2. INTRODUCTION AND BACKGROUND

2.1. Background of the Condition/Standard of Clinical Care

Alport syndrome is a rare genetic disease caused by mutations in genes encoding the alpha-3, alpha-4, and/or alpha-5 chains of type IV collagen found in the basement membranes of kidney glomeruli, cochleae, and eyes. The impaired production of alpha chains leads to disruption of the collagen matrix and abnormal basement membrane structure and function, leading to progressive loss of kidney function and kidney failure, sensorineural deafness, and ocular abnormalities associated with loss of vision in some patients.

Approximately 80% of patients with AS have X-linked mutations in the COL4A5 gene, followed by autosomal dominant or recessively inherited mutations in the COL4A3 or COL4A4 genes, and digenic inheritance of concomitant mutations in COL4A3, COL4A4, and/or COL4A5. Disease severity and rate of progression to kidney failure varies based on the type of mutation and its location in the gene. Males

with X-linked AS typically present with hematuria in childhood, develop proteinuria and hypertension in adolescence, and eventually progress to kidney failure requiring dialysis and/or kidney transplant in the second to third decades of life. In general, mutations that lead to loss of alpha chain expression, for example deletions, frame shift mutations, and nonsense mutations, cause a more severe phenotype with more rapid progression to kidney failure in males with X-linked AS and males and females with autosomal recessive AS. Heterozygous mutations in autosomal dominant AS are associated with wide variations of disease manifestations, but generally progress to kidney failure more slowly and later in life, and extrarenal manifestations are less common than in X-linked or autosomal recessive AS.

Current therapies are non-specific and aim to slow progression to kidney failure using angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. There are no approved pharmacologic treatments for AS. Patients with advanced kidney failure require dialysis and/or kidney transplant. Most patients do well after kidney transplant, but approximately 2% to 5% of patients with X-linked or autosomal recessive AS develop anti-glomerular basement membrane antibodies after transplant, often leading to loss of the transplant kidney.

On August 3, 2018, the National Kidney Foundation and Alport Syndrome Foundation held an Externally Led Patient-Focused Drug Development Meeting on AS (National Kidney Foundation and Alport Syndrome Foundation 2018). At that meeting, participants shared their experiences and perspectives regarding the symptoms and burdens of AS and the impact on their daily lives, their perspective on available therapies for AS and their experiences with these treatments, their aspirations for new treatments, and factors that influence their decision to participate in clinical trials for AS. When asked what the most important benefit of a future treatment would be, participants indicated that they were most interested in a medication that slows, stabilizes, or reverses the decline in kidney function and eliminates the need for dialysis or a kidney transplant.

2.2. Pertinent Drug Development and Regulatory History

Bardoxolone is an orally administered triterpenoid cytoprotective agent that binds Kelch-like ECH-associated protein 1 (Keap1). This permits translocation of Nrf2 to the cell nucleus, allowing transcription of a plethora of genes including pro- and anti- inflammatory genes. The precise mechanism of action of bardoxolone is unknown. Bardoxolone is proposed to inhibit immune-mediated inflammation and oxidative stress by up-regulating the antioxidant response, suppressing proinflammatory signaling, reducing mitochondrial reactive oxygen species production, and reducing reactive oxygen species-mediated activation of inflammatory signaling complexes. Through these actions, the Applicant hypothesizes that bardoxolone will decrease inflammation and fibrosis in the kidney and improve kidney function in patients with CKD. The Applicant is developing bardoxolone for the treatment of CKD caused by AS, and has conducted one study, the phase 3 part of Study 402-C-1603 (CARDINAL Phase 3), to support the proposed indication. The Applicant is also evaluating bardoxolone as a treatment for other causes of chronic kidney disease. As discussed elsewhere in the briefing document, a phase 3 trial in patients with diabetic kidney disease was terminated early because of safety concerns.

During the course of development, the FDA voiced concern about the design of CARDINAL Phase 3 and specifically the ability of the trial, as designed, to differentiate bardoxolone's pharmacodynamic effect

on kidney function from its effect on disease progression. For further discussion of this issue and other concerns raised by the Agency, see Appendix 6.1.

3. SUMMARY OF ISSUES FOR THE AC

3.1. Efficacy Issues

In support of the proposed indication, the Applicant conducted a randomized, double-blind, placebo-controlled study in patients with AS (CARDINAL Phase 3). The study met its prespecified primary and key secondary endpoints, which assessed on-treatment and off-treatment changes in eGFR. A key review issue is whether the observed effects on eGFR indicate that bardoxolone slows the loss of kidney function in patients with CKD caused by AS.

The FDA review team recognizes that there is significant unmet need for treatments that can slow the loss of kidney function in patients with AS and reduce the risk of progression to failure. The FDA review team also recognizes that the law allows for regulatory flexibility in determining what constitutes substantial evidence of effectiveness to the extent that such approaches are scientifically valid and do not compromise our regulatory standards of effectiveness. However, for the reasons discussed in this memorandum, the FDA review team does not believe the submitted data demonstrate that bardoxolone is effective in slowing the loss of kidney function in patients with AS and reducing the risk of progression to kidney failure. In addition to the concerns with CARDINAL Phase 3, there are no data in this application from an animal model of Alport syndrome or other adequate and well-controlled clinical trials in AS or CKD that show that bardoxolone slows the loss of kidney function. The FDA is convening this Advisory Committee Meeting to discuss these issues further.

3.1.1. Sources of Data for Efficacy

Principal support for efficacy is provided by Study 402-C-1603 (CARDINAL Phase 3).[1] Data from other studies, including CARDINAL Phase 2 and two studies in patients with T2D and CKD – Study RTA402-005 (TSUBAKI) Phase 2 and Study 402-C-1102 Phase 2 – were also used by FDA to assess the time-course for resolution of bardoxolone's reversible PD effect on kidney function. For an overview of these studies, see Appendix 6.2.

CARDINAL was an international, multicenter, phase 2/3 study that studied the safety, tolerability, and efficacy of bardoxolone in patients with AS. The study included two cohorts: an open-label, single-arm, phase 2 cohort that enrolled 30 patients in the US and a subsequent double-blind, randomized, placebo-controlled, phase 3 cohort that enrolled 157 patients globally. Patients in CARDINAL Phase 3 were randomized 1:1, stratified by baseline urinary albumin-to-creatinine ratio (UACR), to bardoxolone or placebo.

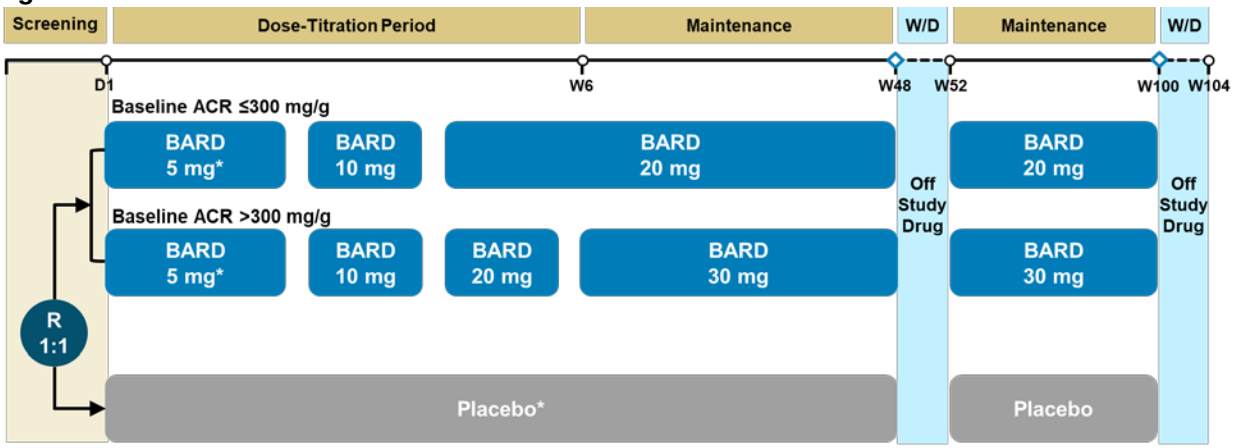
Following randomization, patients were initiated on a dose of 5 mg once daily (adults) or 5 mg every other day (patients 12 years to less than 18 years of age), which was titrated to a maximum dose of

[1] The Applicant also cites data from CARDINAL Phase 2 and Study 1803 (EAGLE), an "extended access study" that primarily aims to provide continuing bardoxolone methyl treatment and assess long-term safety and tolerability, as "supportive" of efficacy. Because these studies are single-arm studies, the cited data are difficult to interpret, and as such, the cited findings are not discussed in this Briefing document.

20 mg in patients with a baseline UACR ≤300 mg/g and a maximum dose of 30 mg in patients with a baseline UACR >300 mg/g. The Applicant based the choice of maximum dose on findings from a short-duration (84 days of dosing) dose-ranging study in patients with diabetic CKD that indicated that patients with a higher baseline UACR required a higher dose to achieve the same reversible PD effect on eGFR as compared to patients with a lower baseline UACR. The dose was titrated because prior experience suggested that tolerability could be improved with gradual dose titration. Patients randomized to placebo underwent sham dose titrations.

After randomization on Day 1, patients were assessed on-site at Weeks 1, 2, 4, 6, 8, 12, 24, 36, 48, 52, 64, 76, 88, 100, and 104 and by telephone contact on Days 3, 10, 21, 31, 38, and 45. Patients did not receive study drug during a 4-week withdrawal period between the Week 48 and Week 52 visits. Patients restarted treatment at Week 52 at the same dose they received at Week 48 and continued study drug through Week 100, with a final follow-up visit at Week 104, see Figure 1.

Figure 1. Schema for CARDINAL Phase 3



◇ Phase 3 primary efficacy analysis.
○ eGFR determination.
* Patients under the age of 18 will receive study drug (BARD or placebo) every other day during Week 1.

Source: Applicant's Orientation Meeting Presentation
Abbreviations: ACR, albumin-to-creatinine ratio; BARD, bardoxolone; D, day; R, randomized; W, week; W/D, withdrew

Analysis visit windows as defined in the statistical analysis plan (SAP) are shown in Table 1. Of note, the analysis windows for the 4-week post-treatment assessment allowed for inclusion of measurements obtained as early as 14 days after drug withdrawal in Year 1 and Year 2.

Table 1. eGFR Analysis Windows for CARDINAL Phase 3

Analysis Window	Study Day[a]	Day After Last Dose	Analysis Window
Week 1	7		2 ≤ SD ≤ 10
Week 2	14		11 ≤ SD ≤ 21
Week 4	28		22 ≤ SD ≤ 35
Week 6	42		36 ≤ SD ≤ 49
Week 8	56		50 ≤ SD ≤ 70
Week 12	84		71 ≤ SD ≤ 126
Week 24	168		127 ≤ SD ≤ 210
Week 36	252		211 ≤ SD ≤ 294
Week 48	336		295 ≤ SD ≤ 350
Week 52[d]		28	14 ≤ day after last dose[b] ≤ 35
Week 64	448		407 ≤ SD ≤ 490
Week 76	532		491 ≤ SD ≤ 574
Week 88	616		575 ≤ SD ≤ 658
Week 100	700		659 ≤ SD ≤ 714
Week 104[e]	-	28	14 ≤ day after last dose[c]

Source: Based on Table 3 in CARDINAL Phase 3 SAP
[a] Relative to the day of randomization
[b] Last dose is week 48 or last dose for permanent discontinuation prior to week 48
[c] Last dose is week 100 or last dose for permanent discontinuation after week 52 and 100. The original analysis window for Week 104 was defined as 14 to 35 days after last dose. It was modified to at least 14 days after last dose in the addendum to SAP dated 30 October 2020.
[d] Must be after the last dose in year 1 but before receiving treatment in year 2
[e] Last dose for week 104 is week 100 or last dose of permanent drug discontinuation after week 52 and prior to week 100.
Abbreviations: eGFR, estimated glomerular filtration rate; SAP, statistical analysis plan; SD, study day

The primary and key secondary study endpoints were as follows:

- Primary: Change from baseline in eGFR at Week 48 (Year 1) and Week 100 (Year 2)
- Secondary: Change from baseline in eGFR following a 4-week drug treatment withdrawal period, at Week 52 (Year 1) and Week 104 (Year 2)

Analyses of efficacy described in this section are the primary analyses of the CARDINAL Phase 3 efficacy endpoints and pertain to the intention-to-treat (ITT) population (i.e., all patients randomized in the phase 3 portion of the study). The Year-1 and Year-2 endpoints are not independent hypothesis sets and were analyzed using a combination of the Bonferroni and fixed-sequence approaches for type 1 error control.

Of note, the Applicant conducted an interim analysis of CARDINAL Phase 3 after all patients have completed their Week 52 visit. In January and September 2020, the Applicant met with the Agency to discuss accelerated approval of bardoxolone based primarily on the results of this interim analysis. As discussed in Appendix 6.2, the Division did not agree with the proposed approach and the Applicant did not pursue accelerated approval.

3.1.2. Efficacy Summary

3.1.2.1. Disposition of Patients

A summary of the patient disposition and the number of patients in each analysis population is shown in Table 2. Between August 2017 and November 2018, 157 patients were randomized: 77 to bardoxolone

and 80 to placebo. Almost all patients completed study follow-up through Week 104 (75 [97%] in the bardoxolone group and 79 [99%] in the placebo group).

A greater proportion of patients discontinued treatment prematurely in the bardoxolone group as compared to the placebo group (34% versus 16%); most of these discontinuations occurred in Year 1. The most common reasons for discontinuation of study medication in the bardoxolone group in Year 1 were adverse events (10%) and "withdrawal" (10%). Of the eight patients in the bardoxolone group categorized as "withdrawal" in Year 1, six were withdrawn from treatment because they met a protocol-specified withdrawal criterion; an additional patient in the bardoxolone group withdrew from treatment because of a protocol-specified withdrawal criterion in Year 2. All the withdrawals due to protocol-specified withdrawal criteria were related to increases in liver transaminases or decline in kidney function. See Section 6.8 for further discussion of the liver findings. No patient in the placebo group discontinued treatment due to a protocol-specified withdrawal criterion in either year.

Table 2. Disposition of Patients

Disposition	Placebo (N=80) n (%)	Bardoxolone (N=77) n (%)
Year 1		
ITT	80 (100)	77 (100)
On Treatment at Week 48	71 (88.8)	60 (77.9)
Discontinued prior Week 48	9 (11.2)	17 (22.1)
AE	4 (5.0)	8 (10.4)
Withdrawal[a]	3 (3.8)	8 (10.4)
LFU	1 (1.3)	1 (1.3)
Other	1 (1.3)	0
Year 2		
Received >=1 dose	69 (86.3)	58 (75.3)
On Treatment at Week 100	67 (83.8)	51 (66.2)
Discontinued prior Week 100	2 (2.5)	7 (9.1)
AE	0	1 (1.3)
Withdrawal[a]	2 (2.5)	3 (3.9)
LFU	0	1 (1.3)
Other	0	1 (1.3)
Completed Follow-up at Week 104	78 (97.5)	75 (97.4)

Source: Reviewer's analysis
[a] Includes withdrawal by patient and withdrawal due to protocol-specified withdrawal criterion. Patients discontinuing bardoxolone due to protocol-specified withdrawal criterion discontinued treatment due to increases in liver transaminases or decline in kidney function.
Abbreviations: AE, adverse events; ITT, intent-to-treat; LFU, lost to follow-up.

3.1.2.2. Demographic and Baseline Characteristics

Overall, the baseline demographic and disease characteristics were reasonably balanced between the treatment groups. The mean age of patients in the placebo group was 40 years (range: 13 to 70 years), and the majority (68 of 80 patients [85%]) were 18 years or older. The placebo group included 12 patients who were under the age of 18 years. Most placebo patients were female (48/80 [60%]) and white (63/80 [79%]). The mean age of patients in the bardoxolone group was 39 years (range: 13 to 65 years), and the majority (66/77 patients [86%]) were 18 years or older. The majority of bardoxolone patients were also female (43/77 [56%]) and white (55/77 [71%]). Most of the patients were enrolled within the US (placebo 69% and bardoxolone 65%).

The mean (range) baseline eGFR was similar in the bardoxolone (62.7 [29.5 to 96.6] mL/min/1.73 m^2) and placebo (62.6 [28.2 to 91.3] mL/min/1.73 m^2) treatment groups. The median (range) baseline UACR was also similar in the two treatment groups (bardoxolone: 205 [2.1 to 3495] mg/g; placebo: 253 [1.2 to 3031] mg/g).

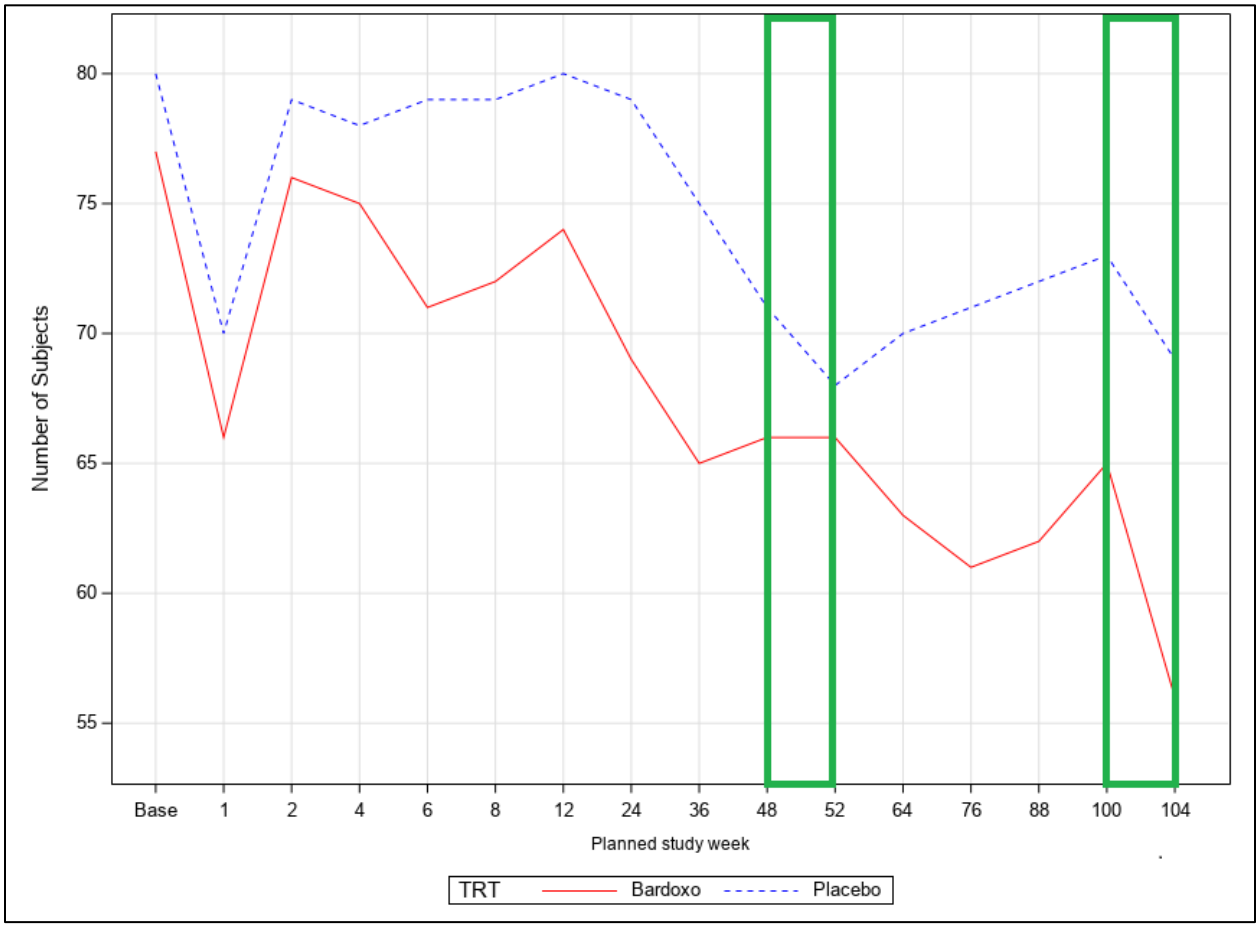
3.1.2.3. Efficacy Results

Primary Efficacy Endpoint

The primary endpoints were the change from baseline in eGFR at Week 48 (Year 1) and Week 100 (Year 2). The primary efficacy endpoints were analyzed used a mixed model for repeated measures without imputation for missing eGFR data; all eGFR values collected through Week 48 or Week 100 were included, regardless of whether a patient was receiving treatment.

Figure 2 shows the number of patients in the bardoxolone and placebo treatment arms who had eGFR values collected within the SAP-defined analysis window for each of the planned study visits. The green bars indicate the 4-week washout periods in Year 1 and Year 2, respectively. In Year 1, 68 patients in the placebo group and 66 in the bardoxolone group had their off-treatment eGFR value collected within the SAP-defined analysis window. In Year 2, more patients (78 in the placebo group and 75 in the bardoxolone group) had an off-treatment eGFR value collected. However, the Year 2 off-treatment analysis only included patients who took at least one dose of study drug in Year 2; those who did not take a dose in Year 2 but had eGFR values collected approximately 104 weeks from randomization were not included in the analysis. In Figure 2, these patients are not included in the 4-week washout period in Week 104.

Figure 2. The Number of Patients With eGFR Values Collected Within the SAP-Defined Analysis Window



Source: Reviewer's analysis
The Year 2 off-treatment period only includes patients who had eGFR values collected in the time window who also took at least one dose of study drug in Year 2 since the Year 2 off-treatment analysis was restricted to patients who took at least one dose of study drug in Year 2.
Abbreviations: Bardoxo, bardoxolone; eGFR, estimated glomerular filtration rate; SAP, statistical analysis plan; TRT, treatment.

The study met its prespecified primary endpoints. Treatment with bardoxolone resulted in a statistically significant change from baseline in eGFR compared to placebo (Table 3), with placebo-corrected differences of 9.2 mL/min/1.73 m^2 ($p < 0.0001$) at Week 48 and 7.4 mL/min/1.73 m^2 ($p = 0.0008$) at Week 100.

Table 3. Change from Baseline in eGFR at Week 48 and Week 100 for Bardoxolone vs. Placebo (ITT population)

Variable	Placebo (N=80)	Bardoxolone (N=77)
Change from baseline at Week 48[a]		
N	71	66
LS mean (SE)	-4.7 (1.3)	4.5 (1.3)
LS mean difference (SE)	9.2 (1.8)	
97.5% CI	5.1, 13.4	
p-value	<0.0001	
Change from baseline at Week 100[a]		
N	73	65
LS mean (SE)	-8.4 (1.5)	-1.0 (1.6)
LS mean difference (SE)	7.4 (2.2)	
95% CI	3.1, 11.6	
p-value	0.0008	

Source: Reviewer's analysis

[a] The change from baseline eGFR in patients treated with bardoxolone methyl is compared with placebo using MMRM analysis without including the post baseline treatment duration factor TRT01DUR or TRT02DUR.

Abbreviations: eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; LS, least squares; SE, standard error; MMRM, mixed model repeated measures

Secondary Efficacy Endpoints

Key secondary endpoints in CARDINAL Phase 3 were the off-treatment change from baseline in eGFR in bardoxolone-treated patients relative to placebo at Weeks 52 and 104. As previously noted, although these endpoints are described as the change from baseline in eGFR following a 4-week drug treatment withdrawal period, the analysis windows for these endpoints allowed for inclusion of measurements obtained as early as 14 days after drug withdrawal. These key secondary endpoints were to be analyzed using an analysis of covariance (ANCOVA) model and used treatment-based multiple imputation for missing eGFR data. The total significance level (0.05) was split between Year 1 and Year 2 as a strategy to reserve alpha to test Year 2 if the Year-1 testing sequence was not statistically significant. If a significant treatment effect was seen for both the primary and secondary Year-1 endpoints, the significance level for Year 1 (0.025) remained available to be carried forward (recycled or passed along) to the Year-2 testing sequence. Thus, since both Year-1 endpoints were significant, the Year-2 testing sequence was tested using a significance level of 0.05.

Treatment with bardoxolone resulted in a significantly higher off-treatment change from baseline in eGFR compared to placebo, with a placebo-corrected difference in the ITT population of 5.4 mL/min/1.73 m^2 (p = 0.0008) at Week 52 and 4.4 mL/min/1.73 m^2 (p = 0.02) at Week 104 (Table 4).

Table 4. Change from Baseline in eGFR at Week 52 and Week 104 for Bardoxolone vs. Placebo

Variable	Placebo (N=80)	Bardoxolone (N=77)
Change from baseline at Week 52[a]		
N	68	66
LS mean (SE)	-6.2 (1.2)	-0.8 (1.2)
LS mean difference (SE)	5.4 (1.6)	
97.5% CI	1.8, 9.1	
p-value	0.0008	
Change from baseline at Week 104[a]		
N	69	56
LS mean (SE)	-9.0 (1.3)	-4.4 (1.5)
LS mean difference (SE)	4.4 (1.9)	
95% CI	0.7, 8.1	
p-value	0.02	

Source: Reviewer's analysis

[a] The change from baseline eGFR in patients treated with bardoxolone methyl is compared with placebo using ANCOVA analysis without including the post baseline treatment duration factor TRT01DUR or TRT02DUR. Missing values are imputed using multiple imputations based on the treatment group to which the patient is assigned, baseline eGFR, and randomized UACR.
Abbreviations: eGFR, estimated glomerular filtration rate; LS, least squares; SE, standard error.

As previously noted, to be included in the Year 2 off-treatment analysis, patients needed to take at least one dose of study drug in Year 2. In the Bardoxolone group, 58 patients took at least one dose of study drug in Year 2 as compared with 69 patients in the placebo group. See Section 3.2.1.2, for the result of a sensitivity analysis that includes all available eGFR values collected approximately 104 weeks after randomization, irrespective of time off study drug.

As also previously noted, the analyses of off-treatment change from baseline in eGFR at Week 52 and Week 104 used ANCOVA, with missing values imputed using multiple imputation based on the assigned treatment group. In brief, this multiple imputation procedure models the distribution of missing values and the validity of the results depends on statistical modeling. Of note, the SAP did not specify which factors were to be included in the imputation step. For the off-treatment analyses, the Applicant's multiple imputation step included one less factor in the Week-104 analysis than in the Week-52 analysis. When a similar factor is included in the multiple imputation step in the Week 104 analysis, the placebo-corrected difference in the off-treatment change from baseline in eGFR at Week 104 is no longer statistically significant (p=0.34). Please refer to Appendix 6.6 for technical details.

The Applicant asserts that inclusion of this third factor in the multiple imputation step for the Week-104 analysis produces a range of eGFR values that disproportionally fall outside of the range of observed values and leads to a standard error of the estimated treatment difference that is 2.4-times larger than that of the observed Week-104 data. The Agency acknowledges the Applicant's explanation; however, loss of statistical significance based on a change in a single factor raises concern about the robustness of the study's findings.

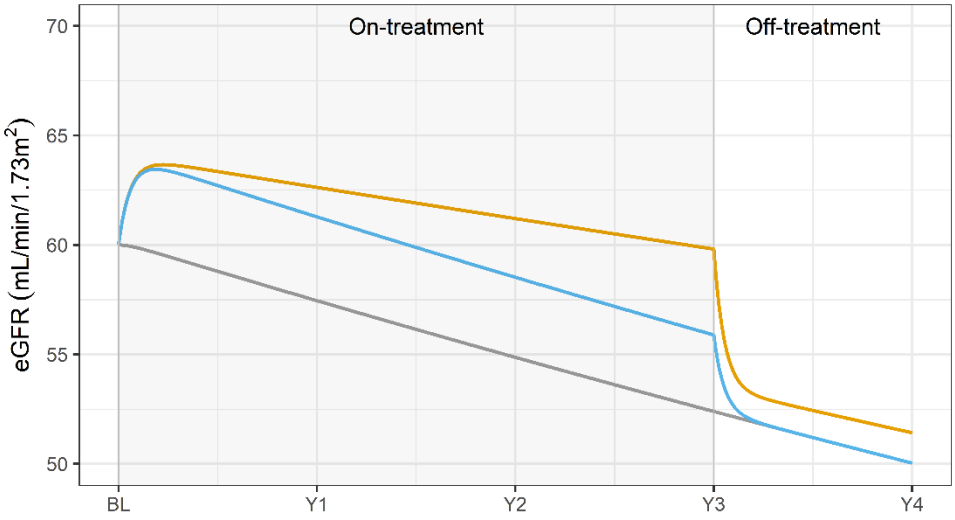
3.2. Efficacy Issues in Detail

3.2.1.1. Issue 1: Adequacy of the design of the CARDINAL Phase 3 study to differentiate between reversible PD effects and slowing of disease progression

Examples of different patterns of treatment effects on eGFR are depicted in Figure 3. A treatment that slows disease progress should change the trajectory of the decline in kidney function (see orange line).

In this situation, after the drug is stopped and the pharmacodynamic effect on kidney function is fully resolved, the eGFR is better than it would have been had no drug been given (see gray line). In contrast, reversible pharmacodynamic treatment effects would change eGFR upon initiation of treatment, but would not change the trajectory of the disease course (see blue line). In this situation, the effect on eGFR disappears in the off-treatment period after the pharmacodynamic effect has fully reversed and the eGFR is the same as it would have been had no drug been given (see gray line). A treatment can have both reversible effects on kidney function as well as change the trajectory of the decline in kidney function (see the orange line), but it can be difficult to tease apart the contribution of each component in trials with short treatment duration and/or when off-treatment measurements of eGFR are obtained before the pharmacodynamic effect on eGFR has fully reversed.

Figure 3. Patterns of Treatment Effects on Kidney Disease Progression



Source: Reviewer's figure
Disease progression describing the natural history using a linear model (solid gray line: analogous to placebo). A treatment effect that shifts the disease progression time-course but is reversible after stopping treatment does not change the trajectory of the disease course (blue line). A treatment effect is considered disease modifying when the treatment changes the time-course of disease progression and the improved kidney function persists after treatment cessation (solid orange line: reversible pharmacodynamic effect and treatment-modifying). Adapted from (Chan and Holford 2001).
Abbreviations: BL, baseline; eGFR, estimated glomerular filtration rate; Y, year.

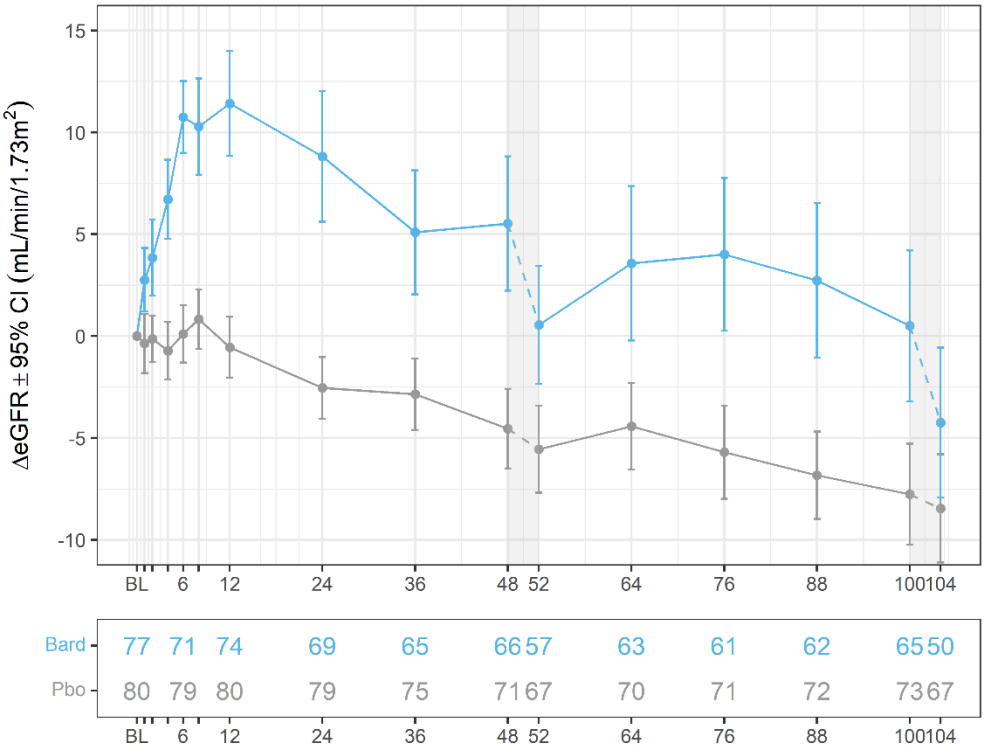
The CARDINAL Phase 3 study consisted of two years of longitudinal on-treatment eGFR assessments with two 4-week washout periods, after Year 1 and Year 2, respectively. The time-course of eGFR changes in the bardoxolone and placebo groups is shown in Figure 4. eGFR increased compared to placebo while on treatment at Week 48 and Week 100, as evaluated by the primary efficacy endpoint; however, eGFR decreased during each of the 4-week washout periods, suggesting that the on-treatment increase in eGFR was, at least in part, a result of the reversible PD effect of bardoxolone on eGFR. If the duration of the washout was long enough to eliminate the reversible PD effect on eGFR, then changes in eGFR compared with placebo at the end of the Year-2 washout period could indicate bardoxolone's effect on slowing disease progression. A key issue was to determine if the study's 4-week washout was long enough for the reversible PD effect on eGFR to have resolved.

The Applicant has justified the 4-week washout in CARDINAL Phase 3 based on: various pooled analyses of patients across studies with eGFR measurements collected up to 42 days off-treatment; off-treatment

eGFR measurements from studies in patients with CKD with treatment duration ≤8 weeks; the pharmacokinetic (PK) profile of bardoxolone; exposure-response modeling; and time to return to baseline of other PD markers, such as liver enzymes. The FDA has not found these justifications compelling to support the adequacy of a 4-week washout in patients with AS, as described in Appendix 6.4.

Therefore, the FDA review team conducted additional analyses to understand the pattern of bardoxolone's treatment effects on eGFR and adequacy of the 4-week washout time-course (see Efficacy Issue 2 [Section 3.2.1.2] and 3 [Section 3.2.1.3], below).

Figure 4. Change From Baseline eGFR by Analysis Window in CARDINAL Phase 3



Source: Reviewer's analysis
Descriptive summary of the change from baseline in eGFR by week for the bardoxolone and placebo groups for the ITT population by analysis window (see Table 1 for definitions), excluding observations carried forward. Dose titration occurred over 4 to 6 weeks in Years 1 and 2. Shaded areas represent 4-week washout periods
Abbreviations: Bard, bardoxolone; BL, baseline; eGFR, estimated glomerular filtration rate; Pbo, placebo.

3.2.1.2. Issue 2: Analyses on pattern of treatment effect and the impact on the eGFR values collected outside the SAP-defined analysis window

When comparing the treatment effects between Week 48 and Week 100 (primary endpoint), the change from baseline in eGFR does not show increasing divergence between treatment and placebo groups. Due to the study design with a washout period at the end of Year 1, a conventional eGFR slope analysis over the 2 years is not possible for CARDINAL Phase 3. A repeated-measures model was therefore used to quantify the treatment group difference by visit to further evaluate whether there is an accrual of benefit over the study duration. The repeated-measures model included treatment group and analysis visit as factors and baseline eGFR as a covariate, and the results are shown in Table 5. The results of this

analysis do not show an increasing divergence of treatment effect, i.e., slowing in decline in kidney function, over the study duration.

Table 5. eGFR Change from Baseline by Analysis Visit

Analysis Visit (Week)	Bardoxolone (N=77) N	Bardoxolone (N=77) LS Mean (SE)	Placebo (N=80) N	Placebo (N=80) LS Mean (SE)	Difference From Placebo in LS mean (SE)
12	74	11.3 (1.3)	80	-0.5 (0.8)	11.8 (1.5)
24	69	8.3 (1.6)	79	-2.5 (0.8)	10.8 (1.7)
36	65	4.7 (1.4)	75	-2.7 (0.9)	7.4 (1.7)
48	66	4.6 (1.6)	71	-4.6 (1.0)	9.2 (1.8)
52	66	-0.8 (1.3)	68	-5.4 (1.1)	4.7 (1.6)
64	63	2.1 (1.8)	70	-4.7 (1.1)	6.8 (2.1)
76	61	2.6 (1.7)	71	-5.7 (1.2)	8.3 (2.1)
88	62	1.8 (1.8)	72	-7.4 (1.1)	9.3 (2.1)
100	65	-0.7 (1.8)	73	-8.6 (1.2)	7.9 (2.2)
104	56	-6.4 (1.6)	69	-8.4 (1.3)	1.9 (2.1)

Source: Reviewer's analysis
Abbreviations: eGFR, estimated glomerular filtration rate; LS, least squares; SE, standard error.

The primary off-treatment analysis in CARDINAL Phase 3 used treatment-based multiple imputation for missing data without including the patients who did not take a single dose in Year 2. This analysis includes observed eGFR data from 80% of all randomized patients. As noted above, this analysis showed a significantly higher off-treatment change from baseline in eGFR compared to placebo, with a placebo-corrected difference in the ITT population of 4.4 mL/min/1.73 m^2 (p = 0.02) at Week 104. We performed a set of additional sensitivity analyses on the Year-2 key secondary endpoint to assess the impact of the analysis window on the interpretation of the CARDINAL Phase 3 key secondary endpoint results by using all available off-treatment data.

The results of these sensitivity analyses are as follows and summarized in Table 6:

- S1: No imputation and excluded the eGFR values collected outside of the analysis window. This analysis includes eGFR data from 80% (125/157) of all randomized patients with no imputation. The results showed that off-treatment change in eGFR relative to placebo continued to favor bardoxolone in Year 2 (4.5 mL/min/1.73 m^2; nominal p = 0.02).
- S2: Included the first eGFR value collected after the last dose, irrespective of time off study drug in Year 2. S-2 includes eGFR data from 96% of all randomized patients. If the first off-treatment value was collected prior to Week 52, this value was carried forward and used as the Week 104 value, otherwise the Year-2 off-treatment value was used. The mean off-treatment change in eGFR relative to placebo by the end of Year 2 was 3.5 mL/min/1.73 m^2 (nominal p = 0.04).
- S3: Evaluated all available eGFR values collected approximately 104 weeks after randomization, irrespective of time off study drug. Last observation carried forward was not used. If a patient had multiple off-treatment eGFR values, the one closest to Week 104 was used. In Year 2, this included data from 96% (150/157) of all randomized patients. In this analysis, the difference between the two treatment arms in the off-treatment change in eGFR at the end of Year 2 was reduced to as low as 1.5 mL/min/1.73 m^2 (nominal p = 0.38).
- S4: Included first off-treatment values more than 28 days after last dose. Missing data were not imputed. In Year 2, this included data from 55% (86/157) of all randomized patients. The difference

in the off-treatment change in eGFR between placebo and bardoxolone at Year 2 was 2.6 mL/min/1.73 m^2 with a nominal p-value of 0.18.

- S5: Included last off-treatment values more than 28 days after last dose. Missing data were not imputed. In Year 2, this included data from 55% (86/157) of all randomized patients. This analysis showed that in the bardoxolone group, the mean change from baseline in eGFR relative placebo was further reduced, with a placebo-corrected difference of 1.2 mL/min/1.73 m^2 and a nominal p-value of 0.51.

Table 6. Sensitivity Analyses of Off-Treatment Change From Baseline in eGFR at Week 104

	Placebo (N=80)	Bard (N=77)	Placebo (N=80)	Bard (N=77)	
Analysis	Contributing N		Change From Baseline eGFR		Difference (nominal p-value)
S1: No Imputation	69	56	-11.0	-6.5	4.5 (0.02)
S2: First off-treatment values	78	72	-10.4	-6.9	3.5 (0.04)
S3: Off-treatment values closest to Week 104	78	72	-10.4	-8.9	1.5 (0.38)
S4: First off-treatment values >28 days after last dose	50	36	-10.6	-7.9	2.6 (0.18)
S5: Last off-treatment values >28 days after last dose	50	36	-9.8	-8.6	1.2 (0.51)

Source: Reviewer's analysis
Abbreviations: Bard, bardoxolone; eGFR, estimated glomerular filtration rate.

Except for the S1 sensitivity analysis, these additional sensitivity analyses were not able to demonstrate results similar in magnitude to those of the original primary off-treatment analysis. The decrease in the magnitude of the treatment effect in these sensitivity analyses raises concerns that the off-treatment analysis window may have meaningfully affected the primary results.

3.2.1.3. Issue 3: Additional analyses conducted to assess adequacy of the washout period

The FDA developed a fit-for-purpose PK/PD model with the primary objective to address the adequacy of the 4-week washout period in CARDINAL Phase 3. The details of the model structure and development are provided in Appendix 6.5.

Comparison of observed off-treatment eGFR to model-predicted off-treatment eGFR across studies used for model development (CARDINAL Phase 3 and TSUBAKI), as well as data only used for model validation (CARDINAL Phase 2 and Study 1102) indicate that the model is fit-for-purpose to predict off-treatment eGFR in patients with AS (Table 7).

The model-predicted time-course during CARDINAL Phase 3 and beyond the last visit (nominal visit Week 104) is shown in Figure 5. This figure shows that the observed time-course (error bars) of eGFR is well described by the model (solid line and shaded area); however, the model under-predicts peak drug effects on eGFR (Week 12). The figure shows that the model predicts that the reversible PD effect on eGFR observed with bardoxolone has mostly resolved around Week 110.

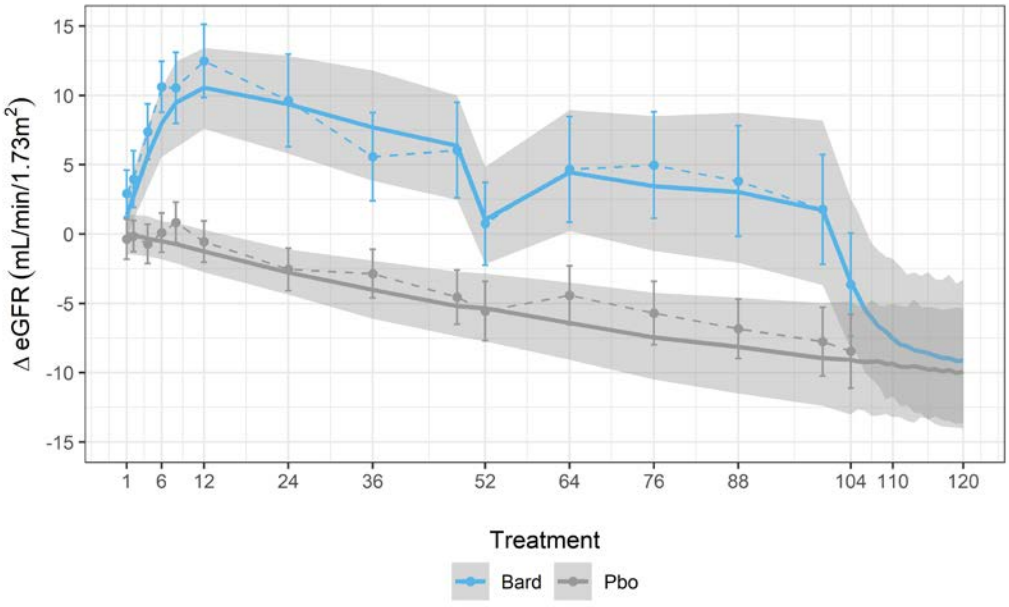
Based on the PK/PD model, it is predicted that at the Week 104 visit, 28% of the reversible PD effect on eGFR remains, and that the time to resolution of the reversible PD effect is 60 days (based on a PD half-life of 15 days, Table 20). This analysis suggests that the duration of the 4-week washout in CARDINAL Phase 3 is insufficient to resolve the reversible PD effect of bardoxolone. This conclusion is consistent with the Applicant's exposure-response model, and neither model suggests that bardoxolone slows the progression of decline in kidney function.

Table 7. Observed vs. Model-Predicted Change in Baseline eGFR During Washout for Bardoxolone

	eGFR (mL/min/1.73m^2) Change From Baseline Mean (95% CI)	
Study Visit	**Observed**	**Predicted**
CARDINAL Phase 3		
Week 52 (Year 1)	0.8 (-2.2 to 3.7)	0.9 (-1.9 to 4.2)
Week 104 (Year 2)	-3.6 (-7.4 to 0.1)	-3.4 (-8.3 to 2.7)
TSUBAKI		
Week 4	3.1 (1.8 to 4.3)	2.7 (1.4 to 4.1)
Week 8	0.5 (-0.8 to 1.8)	0.8 (-0.5 to 1.9)
Study 402-C-1102		
Week 4	0.5 (-1.9 to 3.0)	1.5 (-0.3 to 3.5)
CARDINAL Phase 2		
Week 52 (Year 1)	1.5 (-2.7 to 5.7)	1.6 (-2.5 to 5.4)
Week 104 (Year 2)	-1.1 (-6.5 to 4.2)	-2.1 (-7.8 to 4.7)

Source: Reviewer's analysis
Abbreviations: eGFR, estimated glomerular filtration rate.

Figure 5. Observed and Predicted Time-Course in eGFR With a Predicted Longer Washout Period in CARDINAL Phase 3.



Source: Reviewer's figure
The dashed line and error bars represent the observed eGFR data in CARDINAL Phase 3 (mean ± 95% confidence interval) and the solid lines and shaded area represents model predicted (mean ± 95% confidence interval).
Abbreviations: Bard, bardoxolone; eGFR, estimated glomerular filtration rate; Pbo, placebo.

3.2.1.4. Issue 4: Impact of COVID-19

During the coronavirus disease 2019 (COVID-19) pandemic, any data that could not be assessed remotely were noted as missing. All protocol deviations due to the impacts of COVID-19 were identified and documented accordingly in the clinical database by the site and the Applicant. The number and percentage of patients with visits impacted by COVID-19 are summarized by visit in Table 8. No visits were impacted before Week 76. Although only one visit was not conducted due to COVID-19, between 15% and 24% of the visits conducted between Weeks 76 and 104 were impacted by COVID-19. The most frequently documented impact of COVID-19 on these study visits included one or more procedures not performed (including lab samples not collected), which was reported for 14-23% of these visits, and a visit conducted out of window, which was reported for 2-5% of these visits. The most commonly impacted visits due to COVID-19 were Week 100 visits, with 37 patients (24%) impacted, followed by Week 104 visits, with 32 patients (20%) impacted.

Table 8. Visits Impacted by COVID-19 (ITT Population)

	Placebo (N=80) n (%)	Bardoxolone Methyl (N=77) n (%)	Overall (N=157) n (%)
Week 76			
Visit Impacted by COVID-19	13 (16.3)	10 (13.0)	23 (14.6)
Visit not conducted due to COVID-19	0	0	0
Visit conducted out of window	3 (3.8)	2 (2.6)	5 (3.2)
One or more procedures not performed	13 (16.3)	9 (11.7)	22 (14.0)
Week 88			
Visit Impacted by COVID-19	17 (21.3)	13 (16.9)	30 (19.1)
Visit not conducted due to COVID-19	0	0	0
Visit conducted out of window	0	4 (5.2)	4 (2.5)
One or more procedures not performed	17 (21.3)	11 (14.3)	28 (17.8)
Week 100			
Visit Impacted by COVID-19	21 (26.3)	16 (20.8)	37 (23.6)
Visit not conducted due to COVID-19	0	1 (1.3)	1 (0.6)
Visit conducted out of window	3 (3.8)	0	3 (1.9)
One or more procedures not performed	21 (26.3)	15 (19.5)	36 (22.9)
Week 104			
Visit Impacted by COVID-19	19 (23.8)	13 (16.9)	32 (20.4)
Visit not conducted due to COVID-19	0	0	0
Visit conducted out of window	4 (5.0)	4 (5.2)	8 (5.1)
One or more procedures not performed	19 (23.8)	12 (15.6)	31 (19.7)

Source: CSR Table 12, verified by reviewer
Abbreviations: ITT, intent-to-treat.

COVID-19 may have impacted treatment visits, data collection, or study drug dispensation. The Applicant's effort to minimize impacts include implementation of alternative methods to collect data for patients who were unable to complete in-clinic visits, adjustment to the Week 104 visit window to accommodate COVID-19 scheduling challenges (e.g., allowing extension of the last dose planned for Week 100 by 4 weeks, and if a patient completed Week 100 late in the window, the Week 104 visit was also adjusted), and change in study medication dispensation method to mail. There are significant discrepancies between the study's findings for both Year-2 on-treatment and off-treatment analyses in the subgroups that completed study pre-COVID versus during-COVID. The pre-COVID subgroup is defined as subjects who had all their visits prior to March 1, 2020. The during-COVID subgroup was about 2-3 times larger than the pre-COVID subgroup and consisted of all subjects who had any visits

post March 1, 2020. The study findings were driven by the during-COVID subgroup, see Table 9 and Table 10. The Applicant conducted completer analyses by COVID subgroups and showed similar results. The reason for these differences remains unclear.

Table 9. Impact of COVID-19 on Change From Baseline in eGFR at Week 100

Week 100 (N=157)	Placebo		Bardoxolone
Pre-COVID (N=47)			
N at baseline (N observed at Week 100)	23 (21)		24 (21)
LS Mean (SE)	-2.2 (4.8)		2.1 (5.4)
Pbo-corrected mean difference (SE)[a]		4.3 (4.5)	
During-COVID (N=110)			
N at baseline (N observed at Week 100)	57 (52)		53 (44)
LS mean (SE)	-11.3 (1.7)		-1.3 (2.0)
Pbo-corrected mean difference (SE)		10.0 (2.4)	

Source: Reviewer's analysis
[a] The change from baseline eGFR for patients treated with bardoxolone is compared with placebo at Week 100 using ANCOVA, with baseline eGFR as covariate and the following fixed factors: treatment group, randomized UACR strata, and geographical location. Missing values are imputed using multiple imputations based on the treatment group to which the patient is assigned, baseline eGFR, and randomized UACR.
Abbreviations: eGFR, estimated glomerular filtration rate; LS, least squares; Pbo, placebo; SE, standard error.

Table 10. Impact of COVID-19 on Change From Baseline in eGFR at Week 104

Week 104 (N=157)	Placebo		Bardoxolone
Pre-COVID (N=41)			
N at baseline (N observed at Week 104)	21 (18)		20 (18)
LS Mean (SE)	-5.2 (6.7)		-5.5 (6.2)
Pbo-corrected mean difference (SE)[a]		-0.3 (3.9)	
During-COVID (N=116)			
N at baseline (N observed at Week 104)	59 (51)		57 (38)
LS mean (SE)	-12.2 (1.5)		-5.7 (1.9)
Pbo-corrected mean difference (SE)		6.5 (2.3)	

Source: Reviewer's analysis
[a] The change from baseline eGFR for patients treated with bardoxolone is compared with placebo at Week 104 using ANCOVA, with baseline eGFR as covariate and the following fixed factors: treatment group, randomized UACR strata, and geographical location. Missing values are imputed using multiple imputations based on the treatment group to which the patient is assigned, baseline eGFR, and randomized UACR.
Abbreviations: eGFR, estimated glomerular filtration rate; LS, least squares; Pbo, placebo; SE, standard error.

3.3. Safety Issues

3.3.1. Sources of Data for Safety

The safety evaluation focused on the CARDINAL Phase 3 study in 157 patients with AS. Because the safety database from CARDINAL Phase 3 is small, data from Study 402-C-0903 (BEACON) in CKD patients with T2D were included in the safety evaluation. In brief, BEACON was a multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 study that compared the efficacy and safety of bardoxolone to that of placebo in patients with Stage 4 CKD (eGFR 15 to <30 mL/min/1.73 m^2) and T2D receiving standard of care. A total of 2185 patients were randomized 1:1 to bardoxolone (20 mg) or placebo. The study was designed to assess the efficacy of bardoxolone relative to placebo in delaying progression to end-stage renal disease (ESRD) and cardiovascular death. However, the study was terminated early based on the Independent Data Monitoring Committee recommendation to stop the study "for safety concerns due to excess serious adverse events (SAEs) and mortality in the

bardoxolone group." The Independent Data Monitoring Committee communicated three primary concerns: 1) a higher rate of all-cause mortality in the bardoxolone group compared to placebo; 2) higher rates of fluid overload-related SAEs including heart failure observed in the bardoxolone group compared with the placebo group, which appeared limited to the first 4 weeks of treatment; and 3) unfavorable benefit-risk profile.

3.3.2. Safety Summary

In CARDINAL Phase 3, the safety database is based on 121 patient-years of exposure to bardoxolone and 144 patient-years of exposure to placebo. The incidence and severity of adverse events were generally similar between treatment groups (Table 11). However, more patients discontinued treatment or had dose modification of study drug in the bardoxolone group compared to placebo (see Appendix 6.7.3). The most common adverse events associated with discontinuation were increases in liver function tests (LFTs), BNP or NT-proBNP, muscle spasms and gastroesophageal reflux disease (Table 24).

Table 11. Overview of Treatment-Emergent Adverse Events, Controlled Trial Safety Population, Placebo-Controlled Period, CARDINAL Phase 3[a]

Event	Bardoxolone N=77 n (%)	Placebo N=80 n (%)	Absolute Risk Difference (95.0% CI)[b]
SAE	8 (10.4)	15 (18.8)	-8.4 (-19.3, 2.6)
Fatal outcome	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Life-threatening	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Requiring hospitalization	5 (6.5)	14 (17.5)	-11.0 (-21.0, -1.0)
Persist or Signif Disability/Incapacity	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Congenital anomaly or birth defect	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Other	2 (2.6)	2 (2.5)	0.1 (-4.8, 5.0)
AE leading to permanent discontinuation	17 (22.1)	4 (5.0)	17.1 (6.7, 27.5)
AE leading to dose modification of study drug	37 (48.1)	17 (21.2)	26.8 (12.5, 41.1)
AE leading to interruption of study drug	23 (29.9)	13 (16.2)	13.6 (0.6, 26.7)
Any AE	75 (97.4)	77 (96.2)	1.2 (-4.3, 6.6)
Severe	9 (11.7)	9 (11.2)	0.4 (-9.5, 10.4)
Moderate	54 (70.1)	49 (61.3)	8.9 (-5.9, 23.7)
Mild	72 (93.5)	73 (91.2)	2.3 (-6.0, 10.5)

Source: Reviewer's analysis
[a] Treatment-Emergent AEs defined as occurring within 30 days
[b] Difference is shown between Bardoxolone and Placebo
Abbreviations: AE, adverse event; SAE, serious adverse event

In CARDINAL Phase 3, there were no deaths or concerning imbalances in the pattern of SAEs in the bardoxolone treated group (Appendix 6.7.2, Table 23).

Common treatment-emergent adverse events and adverse events of special interest observed in CARDINAL Phase 3 and BEACON are shown in Table 12 by study and treatment (see Appendix 6.7 for additional details).

Table 12. Common Treatment-Emergent Adverse Event and Adverse Events of Special Interest Observed in CARDINAL Phase 3 and BEACON, Safety Population

	CARDINAL Phase 3		BEACON	
Event	Bardoxolone N=77 n (%)	Placebo N=80 n (%)	Bardoxolone N=1092 n (%)	Placebo N=1093 n (%)
Heart failure (PT)[a]	0 (0)	0 (0)	92 (8.4)	52 (4.8)
Peripheral edema (FMQ[b])	14 (18.2)	14 (17.5)	237 (21.7)	204 (18.7)
Systemic hypertension (FMQ[b])	8 (10.4)	9 (11.2)	137 (12.5)	116 (10.6)
NT-proBNP / BNP increase (PT)[c]	12 (15.5)	5 (6.3)	2 (0.2)	1 (0.1)
Proteinuria / albuminuria (PT)	10 (13)	8 (10)	22 (2)	11 (1)
Hepatic injury (FMQ[b])	41 (53.2)	2 (2.5)	96 (8.8)	16 (1.5)
Weight decrease (PT)	10 (13)	1 (1.2)	222 (20.3)	43 (3.9)
Decreased appetite (PT)	3 (3.9)	1 (1.2)	210 (19.2)	87 (8.0)
Dysgeusia (FMQ[b])	7 (9.1)	2 (2.5)	146 (13.4)	20 (1.8)
Muscle spasms (PT)	38 (49.4)	27 (33.8)	460 (42.1)	169 (15.5)
Hypomagnesaemia (PT)[d]	4 (5.2)	3 (3.8)	235 (21.5)	61 (5.6)
Anemia (FMQ[b])	5 (6.5)	1 (1.2)	103 (9.4)	58 (5.3)
Nausea (PT)	13 (16.9)	11 (13.8)	211 (19.3)	160 (14.6)
Vomiting (PT)	7 (9.1)	3 (3.8)	126 (11.5)	91 (8.3)

Source: Reviewer's analysis
[a] Preferred terms: Cardiac failure and Cardiac failure congestive
[b] FDA Medical Query (version 2020_01_29)
[c] Preferred terms: Brain natriuretic peptide increased and N-terminal prohormone brain natriuretic peptide increased
[d] Preferred terms: Hypomagnesaemia and Blood magnesium decreased
Abbreviations: BNP, brain natriuretic peptide; FMQ, FDA Medical Query; PT, preferred term

Bardoxolone caused changes in a variety of laboratory parameters (see Appendix 6.7 for additional details) and vital signs. The mechanism(s) for these observed changes are not well understood. Bardoxolone caused:

- Increases in N-terminal proB-type natriuretic peptide (NT-proBNP), liver enzymes (i.e., aspartate aminotransferase [AST], alanine aminotransferase [ALT]), UACR, urinary albumin, serum potassium, ferritin, and blood pressure (BP)
- Decreases in serum magnesium, creatinine kinase, hematocrit, hemoglobin, and body weight

The increase in liver enzymes did not coincide with an increase in bilirubin, and no Hy's Law cases were observed. The increase in liver enzymes subsided with continued dosing and resolved during the washout suggesting the possibility of enzyme induction without significant liver injury (see Appendix 6.8 for additional details).

Potential risks of bardoxolone include:

- Increased UACR, increased BP, and decreased body weight. As discussed below, these risks may have implications for the long-term safety of bardoxolone. Bardoxolone's effect on albuminuria and blood pressure also raise concern about efficacy (i.e., that use of bardoxolone over the long term could have deleterious effects on kidney function accelerate progression to kidney failure).
- Heart failure. There were no cases of heart failure in CARDINAL Phase 3, but the study was designed to exclude patients with a history of heart failure or cardiac disease, elevated concentration of B-type natriuretic peptide (BNP) (>200 pg/mL), and extremely compromised kidney function (Stage 4 CKD and UACR >3500 mg/g).

3.3.3. Safety Issues in Detail

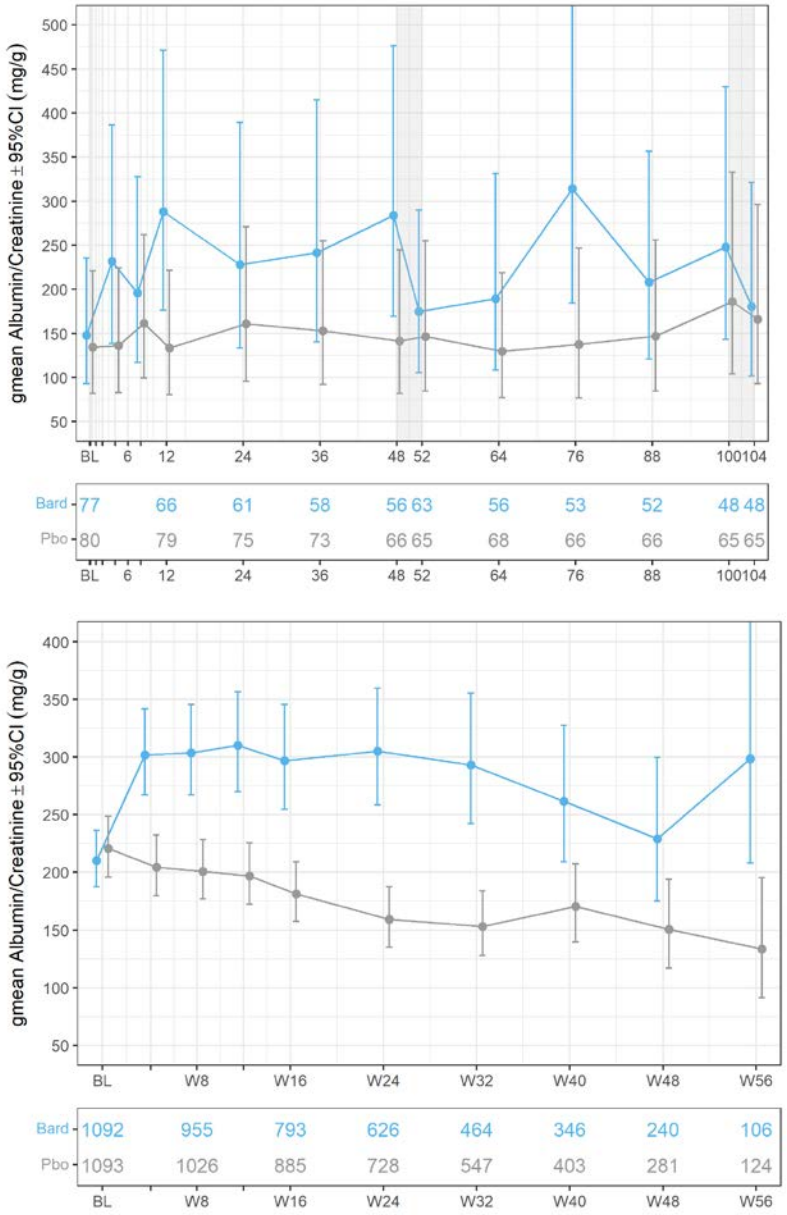
3.3.3.1. Issue 1: Bardoxolone increases albuminuria

Albuminuria can be a marker of kidney damage and epidemiologic data demonstrate a graded relationship between the quantity of albumin in the urine and adverse kidney and cardiac outcomes.

In both CARDINAL Phase 3 and BEACON (Figure 6), initiation of bardoxolone was associated with an increase in albuminuria. While the mechanism behind the observed changes in UACR with bardoxolone are not well understood, it is possible that the changes could be due to an increase in intraglomerular pressure, which, over the long term, could have a deleterious impact on disease progression.

In CARDINAL Phase 3, the increase from baseline in UACR in the bardoxolone arm was similar at Week 48 and Week 100 as shown in Table 13, using a repeated measures model including treatment group and analysis visit as factors and log UACR at baseline as covariate. UACR values decreased towards baseline during each of the two 4-week washout periods. The placebo-corrected increase on treatment was less in year 2 compared to year 1. The increase in UACR with bardoxolone was observed in both baseline UACR subgroups (≤300 mg/g versus >300 mg/g) and in pediatric patients. The incidence of adverse events related to proteinuria and albuminuria was similar between treatment groups in CARDINAL Phase 3 (Appendix 6.7, Table 27).

Figure 6. Geometric Mean UACR Over Time for CARDINAL Phase 3 (Top) and BEACON (Bottom)



Source: Reviewer's figure
Blue lines – bardoxolone; gray lines – placebo
Abbreviations: Bard, bardoxolone; BL, baseline; Pbo, placebo; UACR, urinary a bumin-to-creatinine ratio; W, week.

Table 13. Mean Log UACR Change at Weeks 48, 52, 100, and 104 (CARDINAL Phase 3, Safety Population)

Analysis Visit (Week)	Bardoxolone (N=77)		Placebo (N=80)		Difference From Placebo in LS Mean (SE)
	N	LS Mean (SE)	N	LS Mean (SE)	
48	56	0.52 (0.13)	66	0.01 (0.12)	0.51 (0.18)
52	63	0.17 (0.12)	65	0.05 (0.12)	0.12 (0.17)
100	48	0.58 (0.13)	65	0.31 (0.12)	0.27 (0.18)
104	48	0.22 (0.13)	65	0.29 (0.12)	-0.07 (0.18)

Source: Reviewer's analysis
Abbreviations: LS, least squares; SE, standard error; UACR, urinary albumin-to-creatinine ratio.

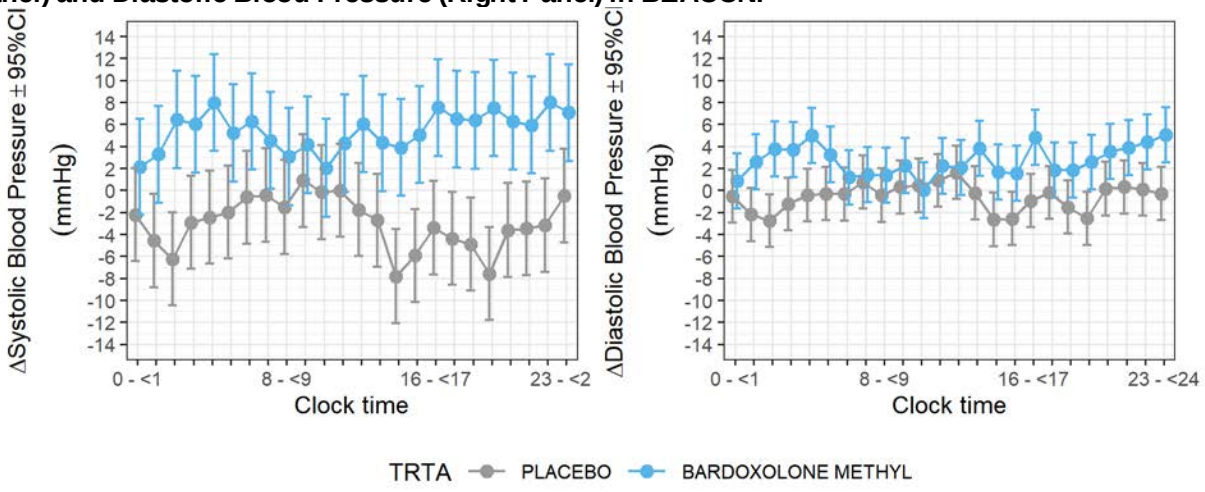
3.3.3.2. Issue 2: Bardoxolone increases blood pressure

Drugs that cause sustained increases in BP are associated with adverse cardiovascular effects. Small elevations of BP of even a few mmHg are a concern when the drug is intended for chronic use, particularly when the target population is at increased cardiovascular risk (May 2018). The FDA recommends use of Ambulatory Blood Pressure Monitoring (ABPM), rather than clinic cuff measurements, when needing to assess whether a drug increases BP because ABPM is capable of detecting small, but potentially relevant, BP effects.

A subset of 174 patients were evaluated in an ABPM sub-study in BEACON. The sub-study collected 24-hour ABPM at baseline and 4 weeks after dosing. Bardoxolone increased both systolic blood pressure (SBP) and diastolic blood pressure (DBP) over 24-hours (Figure 7). The mean increase in the average 24-hour SBP and DBP over baseline was 5.3 mmHg (95% CI: 2.4 to 8.1 mmHg) and 2.6 mmHg (1.2 to 4.0 mmHg), respectively, for bardoxolone compared to -2.9 mmHg (-5.6 to -0.1 mmHg) and -0.5 mmHg (-1.8 to 0.8 mmHg), respectively, for placebo. Similar increases in both daytime and nighttime BP were observed (Figure 8).

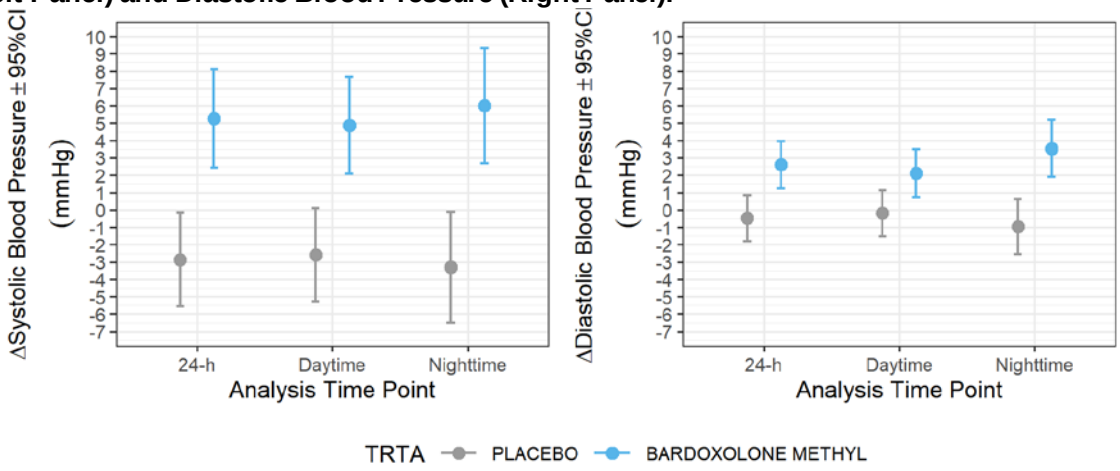
In the safety population of BEACON, an increase in (mean [SD]) SBP (bardoxolone: 1.9 [14] mmHg; placebo: -0.4 [13.4] mmHg) and DBP (bardoxolone: 1.4 [7.4] mmHg; placebo: -0.5 [7.2] mmHg) was also observed in routine, clinic BP measurements at Week 4 (ABPM visit), but the magnitude of increase in BP was less than that observed in the ABPM sub-study.

Figure 7. Time-Course of the Change From Baseline at Week 4 in Systolic Blood Pressure (Left Panel) and Diastolic Blood Pressure (Right Panel) in BEACON.



Source: Reviewer's analysis
Abbreviations: TRTA, actual treatment.

Figure 8. Change From Baseline in 24-h Average, Daytime, and Nighttime Systolic Blood Pressure (Left Panel) and Diastolic Blood Pressure (Right Panel).



Source: Reviewer's analysis
Abbreviations: TRTA, actual treatment.

In the safety population of CARDINAL Phase 3, the mean change from baseline in clinic SBP and DBP was not significantly different between the bardoxolone and placebo groups; however, CARDINAL Phase 3 may not have had the ability to detect small increases in BP. The study used clinic BP measurements, which are associated with measurement error and increased variability, and due to its small size, is not sufficiently powered to detect small, but potentially clinically meaningful increases in BP.

Patients with AS, in general, are younger and have fewer cardiovascular risk factors, but the significance of the sustained increases in BP on kidney function with chronic use of bardoxolone is not known.

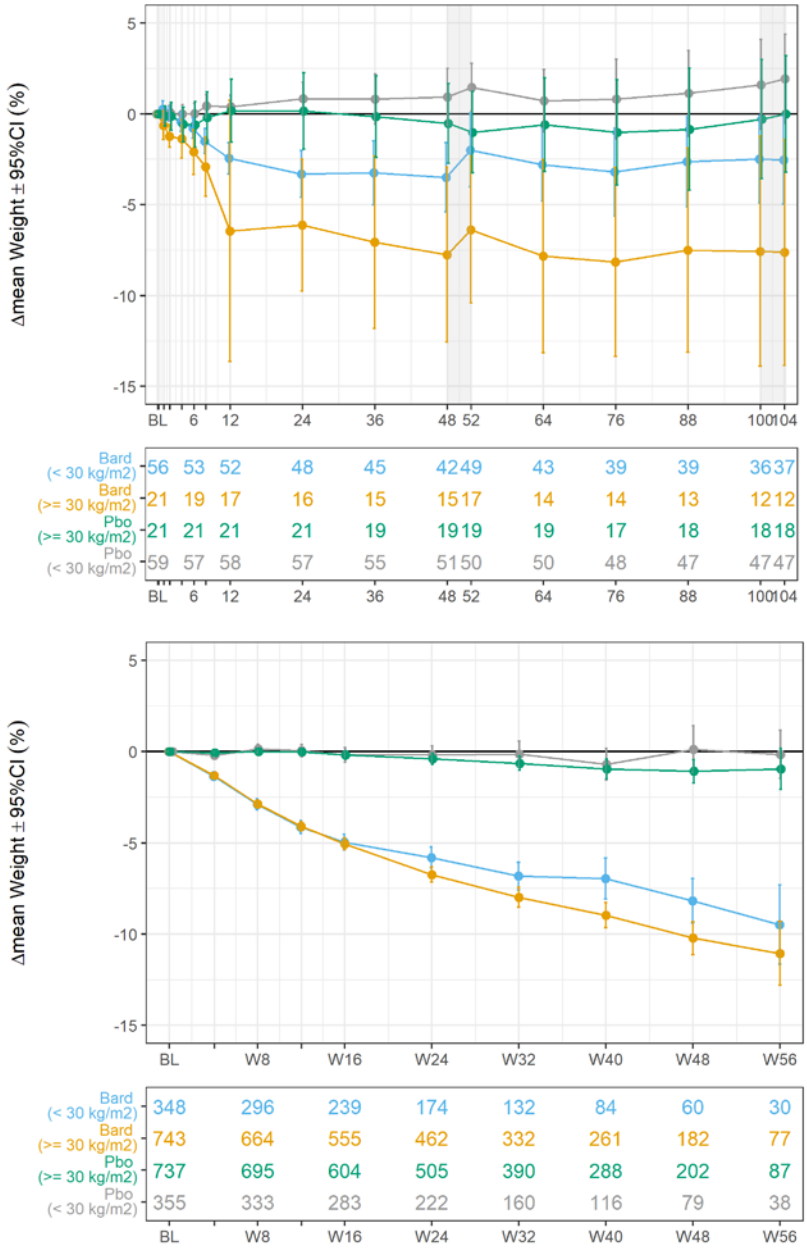
3.3.3.3. Issue 3: Weight changes in pediatric patients

A decrease in body weight was observed in adult and pediatric patients in CARDINAL Phase 3 and in adult patients in BEACON (Figure 9). The magnitude of weight loss was proportional to baseline body mass index (<30 kg/m^2 versus ≥30 kg/m^2). The decrease in body mass index follows a similar time-course to that of the changes in weight. The mechanism for the weight loss is poorly understood. Factors that could have contributed to the observed weight loss include gastrointestinal adverse reactions (decreased appetite, nausea, vomiting, diarrhea, dysgeusia and constipation were more frequent in bardoxolone-treated patients than in placebo), or decreased muscle mass (creatine kinase levels trended lower in bardoxolone-treated patients compared to placebo).

In CARDINAL Phase 3, mean decreases in weight were apparent by Week 6, continued through Week 12, and tended to plateau between Weeks 12 through 100. At Week 100, bardoxolone-treated patients had a mean ± SD weight change from baseline of -3.2 ± 6.5 kg (median -2.2 kg) versus 0.3 ± 5.6 kg (median 0.8 kg) in placebo-treated patients.

Ten (13%) patients treated with bardoxolone reported a treatment-emergent adverse event of 'Weight decreased' compared to 1 (1.3%) placebo-treated patient (Table 12). One of the 10 patients treated with bardoxolone was a pediatric patient. There were no study drug interruptions, study drug discontinuations, or SAEs due to weight loss.

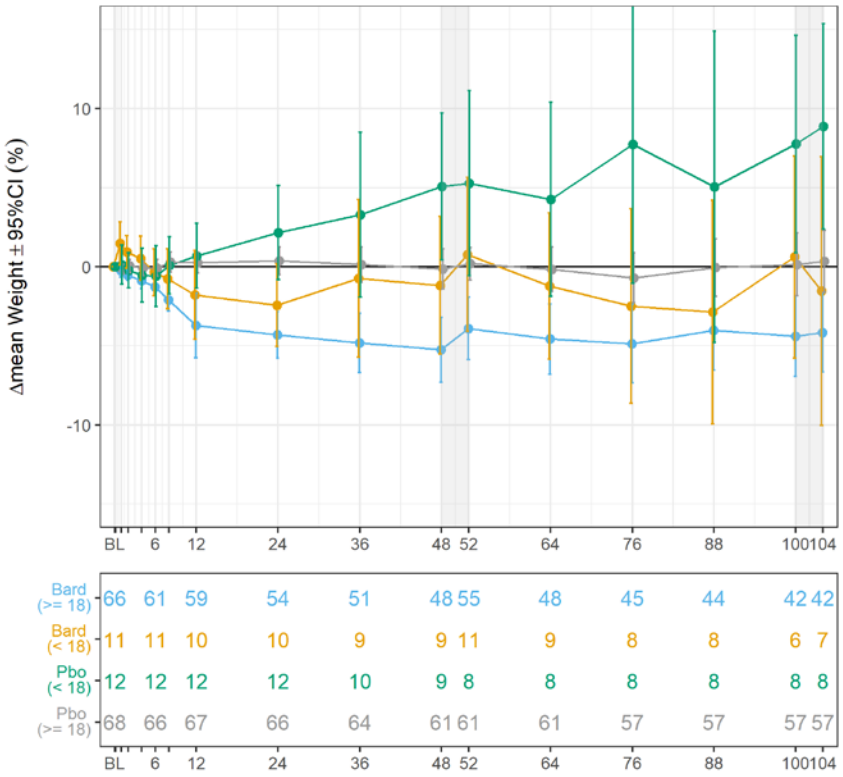
Figure 9. Percent Change in Body Weight Relative to Baseline for CARDINAL Phase 3 (Top) and BEACON (Bottom)



Source: Reviewer's analysis
Abbreviations: Bard, bardoxolone; BL, baseline; Pbo, placebo; W, week.

The pediatric sub-population had an increase in weight in the placebo group, but not in the bardoxolone-treated group (Figure 10 and Appendix 6.7.6). Due to the uncertainty about the cause of the weight loss and the small sample size of the pediatric sub-population, it is not possible to conclude whether weight loss or the inability to gain weight in pediatric patients has the potential to affect their growth and development.

Figure 10. Percent Change in Body Weight Relative to Baseline in Pediatric (<18 Years) and Adult Subgroups in CARDINAL Phase 3



Source: Reviewer's analysis
Abbreviations: Bard, bardoxolone; BL, baseline; Pbo, placebo; W, week.

4. BENEFIT-RISK FRAMEWORK

Disclaimer: This pre-decisional Benefit-Risk Framework does not represent the FDA's final benefit-risk assessment or regulatory decision.

	Evidence and Uncertainties	Comments to the Advisory Committee
Analysis of Condition	• AS is a genetic disease caused by mutations in genes encoding the alpha-3, alpha-4, and/or alpha-5 chains of type IV collagen found in the basement membranes of kidney glomeruli, cochleae, and eyes. The impaired production of alpha chains leads to disruption of the collagen matrix and abnormal basement membrane structure and function, resulting in progressive nephropathy and kidney failure, sensorineural deafness, and ocular abnormalities affecting the lens, retina, and cornea, which can lead to vision loss in some patients. • AS is a rare disease. Medical claims data suggest that there are approximately 14,000 patients with AS in the US; gene frequency studies suggest a US prevalence of 30,000 to 60,000. • Disease severity and rate of progression to kidney failure vary based on the type of mutation and its location in the gene.	AS is a rare, serious, genetic disease that can lead to progressive loss of kidney failure, as well as other complications, including sensorineural hearing loss and loss of vision in some patients.
Current Treatment Options	• There are no approved pharmacologic treatments to slow the progressive loss of kidney function and reduce the risk of kidney failure in patients with AS. • Current therapies are non-specific and aim to slow progression to kidney failure using angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. • Patients who progress to kidney failure require dialysis and/or kidney transplant.	There are no approved treatments to slow the progressive loss of kidney function and reduce the risk of kidney failure in patients with AS; as such, there is significant unmet medical need.

	Evidence and Uncertainties	Comments to the Advisory Committee
Benefits	• CARDINAL Phase 3 was a randomized, double-blind, placebo-controlled study in patients 12 years and older with AS. • The trial met its prespecified primary and key secondary endpoints, which assessed on-treatment and off-treatment changes in kidney function (i.e., eGFR). Treatment with bardoxolone resulted in a statistically significant change from baseline in eGFR compared to placebo, with placebo-corrected differences of 9.2 mL/min/1.73 m^2 ($p < 0.0001$) at Week 48 and 7.4 mL/min/1.73 m^2 ($p = 0.0008$) at Week 100. Treatment with bardoxolone also resulted in a significantly higher off-treatment change from baseline in eGFR compared to placebo, with a placebo-corrected difference in the ITT population of 5.1 mL/min/1.73 m^2 ($p = 0.002$) at Week 52 and 4.3 mL/min/1.73 m^2 ($p = 0.02$) at Week 104. • Because bardoxolone causes a reversible pharmacodynamic increase in eGFR, the FDA review team conducted further analyses to assess: the pattern of bardoxolone's treatment effects on eGFR, the sensitivity of the key secondary endpoints to the off-treatment analysis window, and the adequacy of the 4-week washout period. These analyses suggest that the off-treatment analysis window used in key efficacy analyses may have meaningfully impacted the results of the off-treatment analyses and that the washout period used in the trial may not have been sufficient to assess for bardoxolone's effect on disease progression. The pattern of bardoxolone's treatment effects on eGFR also suggest that even if bardoxolone provides a benefit as relates to the loss of kidney function, it is a one-time benefit that manifests shortly after initiating treatment and does not grow over time, calling into question the benefit of starting treatment at an early stage of disease.	On August 3, 2018, the National Kidney Foundation and Alport Syndrome Foundation held an Externally Led Patient-Focused Drug Development Meeting on AS (National Kidney Foundation and Alport Syndrome Foundation 2018). At that meeting, participants indicated that they were most interested in a medication that slows, stabilizes, or reverses the decline in kidney function and eliminates the need for dialysis or a kidney transplant. CARDINAL Phase 3 met its prespecified primary and key secondary endpoints, which assessed on-treatment and off-treatment changes in kidney function (i.e., eGFR). Key issues include whether the results of the trial demonstrate that bardoxolone slows the loss of kidney function in patients with AS and whether it is reasonable to conclude, based on the available data, that chronic bardoxolone use will reduce the risk of progression to kidney failure in patients with AS. **<u>Points to Consider</u>** Discuss the following: • Whether CARDINAL Phase 3 was adequately designed to assess for bardoxolone's effect on progression of kidney disease • Whether the available data indicate that bardoxolone slows the progression of kidney disease and whether it is reasonable to conclude, based on the available data, that chronic bardoxolone use will reduce the risk of progression to kidney failure in patients with AS
Risks and Risk Management	• Due to the small sample size of CARDINAL Phase 3, safety data from BEACON, a phase 3 study in a related patient population (Patients with T2D and stage 4 CKD) were included in the safety assessment.	Bardoxolone causes changes in a variety of laboratory parameters and vital signs. The mechanisms by which bardoxolone causes these changes are not well understood.

	Evidence and Uncertainties	Comments to the Advisory Committee
	• Potential risks of bardoxolone include: o <u>Increased albuminuria, increased BP, and decreased body weight</u>. Bardoxolone's effect on albuminuria and blood pressure raise concern that, over the long term, bardoxolone use could accelerate progression to kidney failure. o <u>Heart failure</u>. Bardoxolone caused heart failure in BEACON. There were no cases of heart failure in CARDINAL Phase 3, but the study was designed to exclude patients with a history of heart failure or cardiac disease, elevated concentration of B-type natriuretic peptide (BNP) (>200 pg/mL), and extremely compromised kidney function (Stage 4 CKD and UACR >3500 mg/g). • Bardoxolone also caused changes in a variety of other laboratory parameters, including liver enzymes (i.e., AST and ALT) in both CARDINAL Phase 3 and BEACON. The increase in liver enzymes did not coincide with an increase in bilirubin, and no Hy's Law cases were observed. The increase in liver enzymes subsided with continued dosing and resolved during the washout, suggesting the possibility of enzyme induction without significant liver injury.	**<u>Point to Consider</u>** Discuss bardoxolone's safety profile. Include discussion of the following: • Do bardoxolone's effects on albuminuria and blood pressure raise concerns about its long-term efficacy and safety in patients with AS? • What are the implications of bardoxolone's effect on body weight for pediatric patients?

Summary of Benefit-Risk

For a drug to be approved for marketing in the United States, the FDA must determine that the drug is effective and that its expected benefits outweigh its potential risks to patients. A benefit-risk assessment for bardoxolone requires careful consideration of the evidence and remaining uncertainties about the key benefits of the product (as demonstrated in the development program) and potential key risks, as well as the ability to adequately mitigate such risks. This assessment should consider the significant unmet need of patients with a disease.

The FDA review team recognizes that there is significant unmet need for treatments that can slow the loss of kidney function in patients with AS and reduce the risk of progression to kidney failure. The FDA review team also recognizes that the law allows for regulatory flexibility in determining what constitutes substantial evidence of effectiveness. However, for the reasons discussed above, the FDA review team does not believe the submitted data demonstrate that bardoxolone is effective in slowing the loss of kidney function in patients with AS and reducing the risk of progression to kidney failure. The FDA is convening this Advisory Committee Meeting to discuss these issues further.

Abbreviations: ALT, alanine transaminase; AS, Alport syndrome; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end state renal disease; GGT, gamma-glutamyl transferase; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio.

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6. APPENDICES

6.1. Regulatory History

Discussions with the Applicant centered around the issues highlighted below. The Applicant declined an end-of-phase 2 meeting with the Agency; nevertheless, the Agency encouraged the Applicant to obtain Agency concurrence on the adequacy and acceptability of the study to support a marketing application. [2]

- *Bardoxolone's pharmacodynamic effect on eGFR and assessing for effects on disease progression:* At a preIND meeting held in October 2016, the Division indicated that because of bardoxolone's pharmacodynamic effect on kidney function, on-treatment assessments of kidney function would be difficult to interpret as a drug effect on disease progression. As such, a post-treatment assessment of creatinine should be used to assess bardoxolone's efficacy in treating the disease. Following submission of the IND in 2016, the Agency repeatedly voiced concerns about the time-course for resolution of bardoxolone's pharmacodynamic effect on creatinine/eGFR following discontinuation of treatment and whether the off-treatment values collected in CARDINAL Phase 3 were in fact capturing an effect on disease progression. The Agency ultimately recommended that the Applicant conduct a separate study to characterize the time course for resolution of bardoxolone's pharmacodynamic effect or modify CARDINAL Phase 3 to obtain the information (i.e., revise the protocol to include additional off-treatment eGFR measurements).
- *Accelerated Approval:* In January and September 2020, the Applicant met with Agency to discuss submission of an NDA for bardoxolone under the accelerated approval pathway based primarily on the Year 1 data on eGFR from CARDINAL Phase 3. The Division did not agree with the proposed approach, voicing concerns about the interpretability of the eGFR findings given the available information on the time course for resolution of bardoxolone's pharmacodynamic effect, as well as the amount of missing data in the bardoxolone arm and lack of clarity on how patients with missing data were handled in key analyses intended to disentangle the drug's pharmacodynamic effect on kidney function from its effect on the irreversible loss of kidney function.
- *Bardoxolone's effects on blood pressure and albuminuria:* At the January and September 2020 meetings with the Applicant, the Agency voiced concern about bardoxolone's effects on blood pressure and albuminuria and whether, over the long term, these effects could accelerate progression to kidney failure.
- *Trial integrity:* In November 2020, the Applicant submitted an addendum to their SAP dated October 30, 2020, and an amended Data Access Plan dated August 28, 2020 for CARDINAL Phase 3. In its December 2020 response to the submission, the Agency expressed concern about the number of individuals with access to patient-level clinical data and individual treatment assignments following the interim analysis of data from Year 1, as well as the late changes to the study's SAP, and provided

[2] FDA provided extensive written feedback on the Applicant's phase 2/3 trial of bardoxolone in patients with Alport Syndrome in December 2016. In September 2018, FDA encouraged the Applicant to request an end-of-phase 2 meeting to discuss the development program and ensure alignment. The Applicant declined, noting that they were running a phase 2/3 trial and were "not seeking input from the Division on the program at this time." In follow-up correspondence sent in February 2019, the Division emphasized the importance of obtaining FDA concurrence that a study intended to support a marketing application was adequate and acceptable for this purpose. The FDA also encouraged the Applicant to submit a written response to the comments in the FDA's December 2016 advice letter and reiterated its offer to meet with the Applicant to discuss the development program and a path forward.

specific recommendations on additional information and analyses that should be included in the Applicant's marketing application to address the integrity of the trial data. [3]

[3] The Applicant included detailed information on data access in their NDA submission. According to the provided information, the Applicant used a conservative documenting access approach such that individuals who might be at risk of being exposed to the unblinded patient level data but might not have accessed the data were also included in the list of individuals with access. The Applicant also argued that the late changes to the SAP were mainly in response to COVID-19. Sensitivity analyses were performed to assess the impact of the SAP Addendum changes to the study results. The changes to the SAP did not appear to have a significant impact on the estimate of the treatment effect or p-value.

6.2. **Studies Used for Efficacy and Safety Evaluation**

Table 14. Studies Used for Efficacy and Safety Evaluation

Trial Identifier	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
402-C-1603 (CARDINAL) Phase 3	Alport Syndrome	Randomized, double-blind, placebo-controlled, parallel-group with 4-week treatment washout	Drug: Bardoxolone Dosage: 5 mg to 20 mg/day; or 5 mg to 30 mg/day Number treated: 77 bardoxolone; 80 placebo Duration: 100 weeks	Primary: change from baseline in eGFR after 48 and 100 weeks Secondary: change from baseline in eGFR at Week 52 and 104 following a 4-week drug treatment withdrawal period	150 planned; 157 enrolled and treated	57 centers in US, Australia, France, Germany, Japan, Spain and United Kingdom
402-C-1603 (CARDINAL) Phase 2	Alport syndrome	Open-label, single arm	Bardoxolone Dosage: 5 to 20 mg/day or 5 to 30 mg/day Number treated: 30 Duration: 100 weeks	Primary: change from baseline in eGFR after 12 weeks of treatment	30 planned, enrolled and treated	16 sites in the US
RTA402-005 (TSUBAKI) Phase 2	CKD and T2D	Randomized, double-blind, placebo-controlled parallel group with 12-week follow-up	Bardoxolone Dosage: 5 to 15 mg/day Number treated: 65 Bardoxolone; 55 placebo Duration: 16 weeks	Primary: safety and change from baseline in eGFR at 16 weeks	108 planned and analyzed (72 with CKD stage 3 and 36 with CKD stage 4)	37 sites in Japan
402-C-1102 Phase 2	CKD and T2D	Open label followed by 28-day follow-up	Bardoxolone Dosage: 20 mg/day Number treated: 24 Duration: 56 days	Primary: Pharmacokinetics Secondary: Safety	24 planned and analyzed	Multicenter

Trial Identifier	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
402-C-0903 (BEACON) Phase 3	CKD and T2D	Randomized, double-blind, placebo-controlled, parallel-group.	Bardoxolone, 20 mg/day Number treated: 1088 bardoxolone; 1097 placebo Duration median: 7 months (stopped early due to safety)	Primary: delaying progression to ESRD and cardiovascular death Secondary: safety of bardoxolone relative to placebo	2185 enrolled and randomized	320 sites worldwide

Source: Reviewer's analysis
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; T2D, type 2 diabetes.

6.3. **Summary of Pharmacology and Toxicology Profile**

The pharmacological and toxicological profile of bardoxolone was established by a nonclinical development program conducted in accordance with international guidances appropriate for a novel, small molecule therapeutic intended for chronic use. Bardoxolone binds to Keap1, which dissociates from Nrf2. This allows Nrf2 to enter the nucleus and subsequently activate a plethora of genes. The precise mechanism of action that may confer benefit for the intended clinical indication is unclear, as are the key genes mediating such effects. The nonclinical toxicology showed a similarity of target organs of toxicity across species, though markedly differing in severity. Cynomolgous monkeys were considered the most relevant species for human risk assessment, based in part on the similarity of the in vivo metabolite profile. The affected organs included primarily the liver, kidneys, and immune system, and the key toxicology findings considered potentially relevant to human risk are described below.

- Liver: Increased liver weights accompanied by transient elevations in hepatobiliary indicators of injury (e.g., AST, ALT, alkaline phosphatase, bilirubin) and microscopic evidence of biliary hypertrophy and hyperplasia were variably observed across multiple nonclinical species, including monkeys.
- Kidney: Increased kidney weights were reported in monkeys and other nonclinical species without clear causality and without evident treatment-related adverse microscopic correlates. There was an increased incidence and severity of spontaneous background findings in minipigs without clinical chemistry correlates. When measured, levels of blood urea nitrogen and serum creatinine were either unchanged or lower than concurrent controls.
- Immune system: Decreased thymus weight with lymphoid depletion was reported in multiple nonclinical species, as well as splenic congestion with generalized lymphoid hyperplasia and follicular lymphoid hyperplasia in monkeys. A reduction in the percentage of mature T cells and changes to monocyte and B-cell counts were additionally observed in monkeys following 6- and 12-months exposure to bardoxolone. These changes likely reflect a mix of secondary effects of stress and a potential direct effect on immune cell populations.

In cynomolgus monkeys, the no-observed adverse effect level was determined to be 30 mg/kg/day, based primarily on adverse microscopic changes in the bile duct at higher doses, which provides an approximately 2-fold safety margin relative to the maximum recommended human dose of 30 mg once daily (QD).

The weight of evidence indicates that bardoxolone is not genotoxic. The Nrf2 signaling pathway is associated with both pro-and anti-tumorigenic activities depending upon the cellular context. While the Nrf2 pathway may offer protection against oxidative stress for non-malignant cells, Nrf2 also provides metabolic support for rapidly proliferating (malignant) cells by increasing key metabolic pathways such as amino acid synthesis. However, no evidence currently exists to demonstrate that Keap1 inhibition or Nrf2 activation alone can cause malignant cellular transformation (Cuadrado et al. 2019). Long-term rodent carcinogenicity studies were not feasible due to overt dose-limiting toxicities, likely related to the formation of a species-specific toxic metabolite; therefore, the carcinogenic potential of bardoxolone remains an unresolved question.

6.4. Review of the Applicant's Justification for 4-Week Washout in CARDINAL Phase 3

The Applicant presented the following data to justify the 4-week washout in CARDINAL Phase 3.

1. Serial off-treatment eGFR data are available from 15 patients who were treated with bardoxolone in five different studies and had off-treatment eGFR values collected in each of the following post-dose periods: 1 to <7, 7 to <14, and 14 to <42 days post-dose. While two patients appear to be outliers in opposite directions, the off-treatment average eGFR values at Day 14 and beyond did not decrease further suggesting resolution of acute PD effects in the first 14 days after last dose.

   FDA comment: The 15 patients are pooled from five different studies, which included different dosing (duration, daily dose, formulation) and patient population (AS and T2D with CKD). Moreover, the off-treatment sampling of eGFR planned in the study protocols in all five studies was a single time-point around 4 weeks after the last dose. Considering the heterogeneity of this subset, the sample size is too small to draw any meaningful conclusion concerning the off-treatment time-course for patients with AS. Notably, the analysis excludes the only study with serial off-treatment collection of eGFR (RTA 402-005 or TSUBAKI), which included serial off-treatment eGFR up to 12 weeks post dose. Results from this study suggest that the time to resolution of eGFR increase is around 8 weeks (Figure 11).

2. All off-treatment eGFR collected up to <42 days (n=652) after the last dose from completed studies show no association between magnitude of off-treatment changes in eGFR and the number of days post-drug discontinuation for values between 14 and <42 days after the last dose.

   FDA comment: This is a pool of eGFR data across seven different studies with different dosing (duration, daily dosing, formulation) and patient populations (AS, T2D with CKD, rare CKD, pulmonary hypertension). Half of the patients in this analysis only contribute a single off-treatment value. It is unclear how the findings of the analysis based on this heterogenous data set, with sparse sampling, supports the adequacy of 4 weeks for patients with AS.

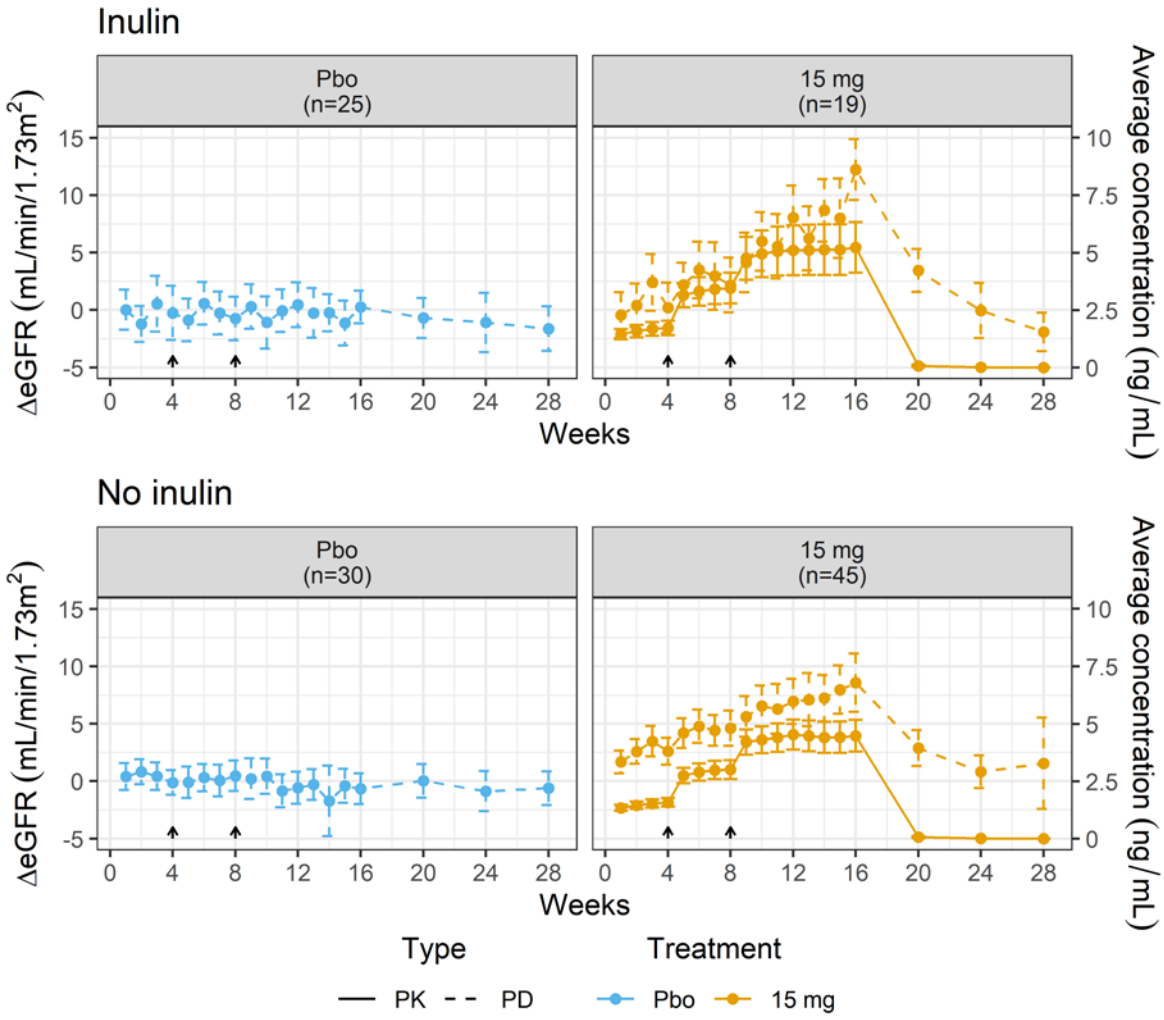
3. Off-treatment eGFR data from studies with treatment duration ≤8 weeks demonstrate that the acute, reversible PD eGFR effects are fully washed out and return to pre-study baseline within four weeks after stopping study drug.

   FDA comment: We agree that these short-term trials in patients with Stage 3-4 CKD show a return to baseline in 4 weeks. The time it takes to return to baseline values could depend on disease characteristics and duration of treatment and may not be the same in AS.

4. *In vitro* pharmacology studies in kidney cells and other cell lines demonstrate that the Nrf2-mediated effects are observed with bardoxolone concentrations as low as 0.8 nM. Based on the population pharmacokinetics (PopPK) model, the time for plasma concentration to fall below 0.8 nM is 16 days.

FDA comment: There is uncertainty about the mechanism of action for bardoxolone. Moreover, the conclusion concerning offset time depends on drug-induced changes in eGFR being directly proportional to bardoxolone concentration, without any delay between the drug's PK and PD effects. The assumed lack of a delay between changes in PK and PD does not appear consistent with the purported mechanism of action for bardoxolone, which includes effects on gene expression. Data from several studies in the Application challenge the Applicant's assumption concerning offset time. For example, RTA 402-005 (TSUBAKI; Figure 11) shows a delay between changes in eGFR and bardoxolone concentration (bardoxolone concentration has returned to zero by 4 weeks after the last dose (Week 16) while eGFR continues to decline and does not return to baseline until 8 weeks after the last dose).

Figure 11. Time-Course of ΔeGFR and Bardoxolone Concentration in TSUBAKI



Source: Reviewer's analysis
Time-course of observed ΔeGFR (left, dashed) and average predicted PK based on the Applicant's population PK model (right, solid) in patients with T2D and CKD (eGFR 15 to 60 mL/min/1.73 m^2), by inulin collection status, TSUBAKI. Vertical arrows indicate dose titrations. Last dose in the study is at week 16.
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Pbo, placebo; PD, pharmacodynamics; PK, pharmacokinetics; T2D, type 2 diabetes.

FDA comment: A delay between time to steady state PK and maximum increase in ΔeGFR was also observed in CARDINAL Phase 3. In this study, the maximum increase in ΔeGFR was observed at 12 weeks after the first dose (Figure 4). Since steady state PK is anticipated to be reached 14 days after the last titration, the steady state PK is reached around Week 6 (20 mg QD) and Week 8 (30 mg QD) (Figure 12). The observed peak increase in ΔeGFR is therefore 4 to 6 weeks after steady state PK is reached.

Altogether, data from TSUBAKI, and CARDINAL Phase 3 suggest that there is a delay between time of reaching steady state for bardoxolone concentration and time of peak increase in ΔeGFR.

5. Results from PopPK exposure-response modeling demonstrate that the increase in eGFR after oral administration is proportional to bardoxolone concentrations in plasma. Based on the 48-hour half-life of the drug, one would predict that it takes approximately 14 days (i.e., 7 half-lives) to achieve a maximal PD effect on eGFR after initiation of dosing, and also approximately 14 days for washout of the PD effects following discontinuation.

FDA comment: We agree that steady-state PK is reached 2 weeks after each titration step but disagree that the Applicant's exposure-response modeling demonstrates that changes in eGFR are proportional to bardoxolone concentration. Moreover, the Applicant's exposure-response model includes a delay in the resolution of the reversible pharmacodynamic effect on eGFR and does not include alteration of the trajectory of disease progression as discussed below. The Applicant's exposure-response model is described as follows:

$$eGFR = eGFR_0 \times e^{-Kprog \times TIME} + SLOPE \times Cp^{HILL}$$

where,

$eGFR_0$ *= Baseline eGFR by patient*

K_{prog} *= Disease progression with an interaction, i.e.,* $K_{prog} = TVK_{prog} * (1 + 2.40 * DAGE)$ *where DAGE is 1 for ≤30 years and 0 for >30 years*

TIME = Time in years

SLOPE = Slope of concentration-response

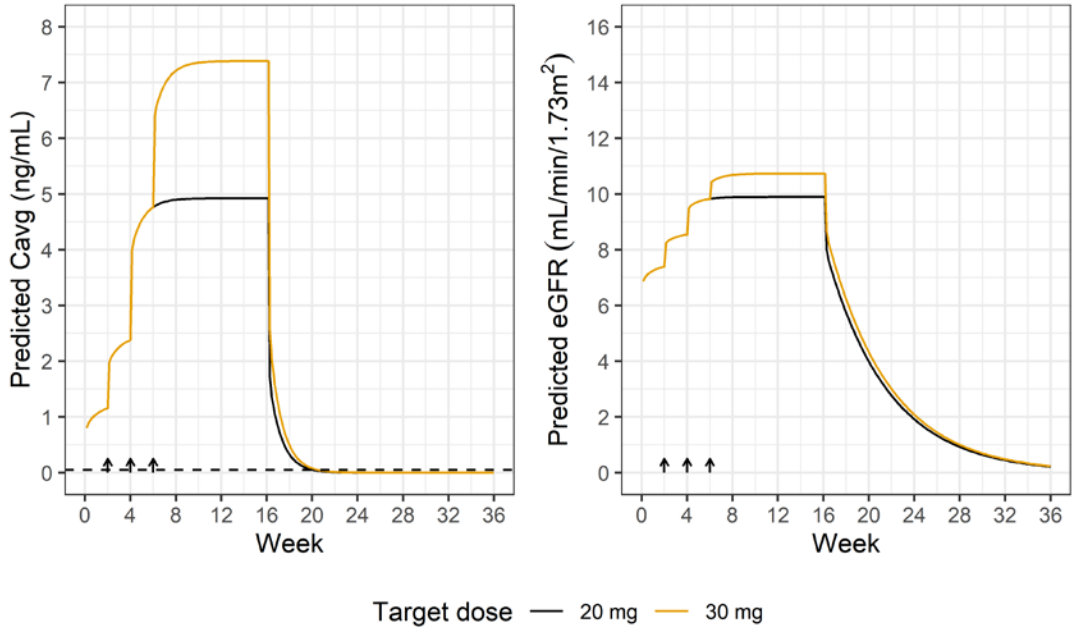
Cp = Bardoxolone concentration (ng/mL)

HILL = Hill coefficient

This model directly conflicts with the assertion that bardoxolone modifies disease progression; disease progression is assumed identical in both treatment arms because there is no interaction between rate of disease progression (K_{prog}*) and treatment.*

*The Applicant's drug effect model is a linear model of bardoxolone concentrations raised to a power of 0.2 (i.e., ΔeGFR = 7.18 * $Cp^{0.201}$ where Cp is bardoxolone concentration). This drug model predicts peak increase in the pharmacodynamic effect on eGFR to occur instantaneously following an increase in bardoxolone concentration and predicts a slow resolution of the increase in eGFR. Figure 12 shows the model-predicted time-course in eGFR based on simulated PK for a typical patient receiving a dose of 20 or 30 mg QD following the titration scheme implemented in CARDINAL Phase 3. The model predicts that the time for eGFR resolution is beyond the 4-week washout implemented in CARDINAL Phase 3. This can be observed by considering that around 4 weeks after the last dose the bardoxolone concentration is near the lower limits of the PK assay (i.e., 0.05 ng/mL) yet the model predicted increase in eGFR is ~4 mL/min/1.73 m^2 corresponding to ~37 to 40% of the peak increase in eGFR for a typical patient per the Applicant's exposure-response model, with continued predicted decline in eGFR thereafter.*

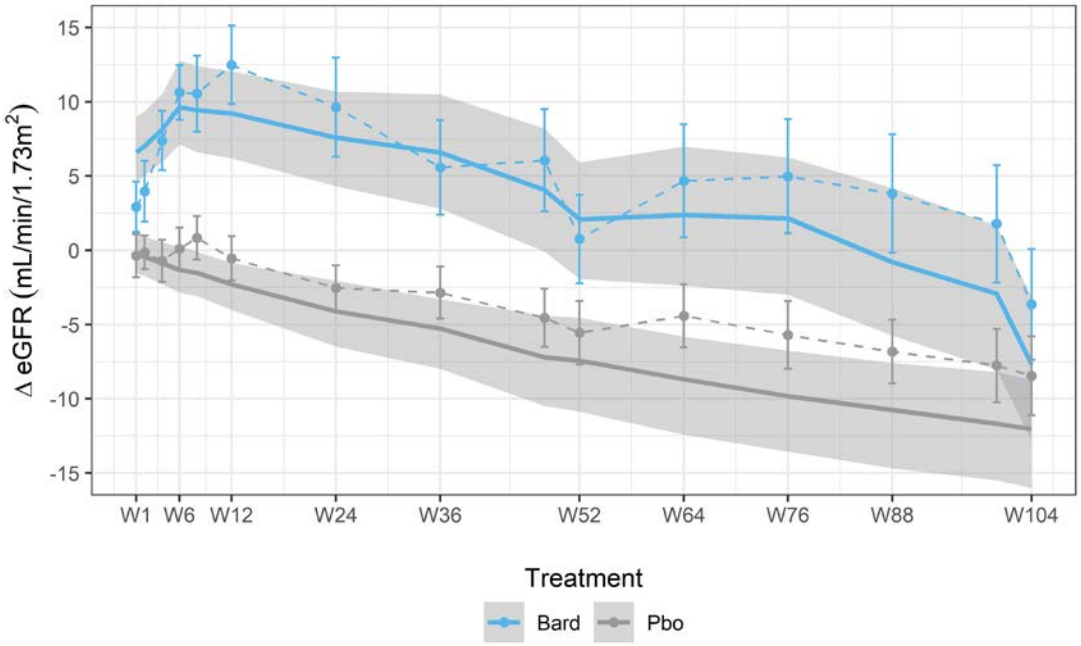
Figure 12. Time-Course of Predicted Bardoxolone Concentration and Change in eGFR for a Typical Patient Using Applicant's Model



Source: Reviewer's analyses
Time-course in bardoxolone concentration (left) and predicted eGFR (right) based on Applicant's PopPK and exposure-response model, respectively, for a typical non-Black male Alport Syndrome Patient (baseline eGFR = 61.6 mL/min/1.73 m^2; Age = 44 years). The time-course is based on a target dose of 20 or 30 mg QD using the titration scheme used in CARDINAL Phase 3 with titration steps represented by vertical arrows. The horizontal dashed line in the left panel represents LLOQ.
Abbreviations: Cavg, average plasma concentration; eGFR, estimated glomerular filtration rate; LLOQ, lower limit of quantification.

Comparison of the model-simulated (solid line and shaded area) time-course of eGFR to that of CARDINAL Phase 3 (error bars) also suggests that the model is not able to capture the onset of changes in eGFR observed during the first 6 weeks (Figure 13).

Figure 13. Simulated Time-Course for eGFR Using Applicant's Exposure-Response Model



Source: Reviewer's analysis
Simulated time-course for ΔeGFR in CARDINAL Phase 3 based on the Applicant's exposure-response model. Solid blue line and shaded gray area represent the model-predicted time-course in mean ΔeGFR and 95% confidence interval compared to the observed mean ΔeGFR and 95% confidence interval represented by the dashed line and error bars.
Abbreviations: Bard, bardoxolone; eGFR, estimated glomerular filtration rate; Pbo, placebo; W, week.

In conclusion, the Applicant's exposure-response model assumes that the increase in eGFR is directly proportional to observed bardoxolone concentration and that there is no disease-modifying effect of bardoxolone on the decline in kidney function. The assumption of the proportional increase in eGFR relative to bardoxolone concentration, without delay, is not consistent with the observed data across multiple studies. Moreover, the lack of any disease progression modification in the model contradicts the Applicant's sought claim of bardoxolone slowing the decline in kidney function.

6. Bardoxolone activates the Nrf2 pathway, which controls the expression of hundreds of genes involved in antioxidative and anti-inflammatory networks. Several Nrf2 transcriptional products, including ALT, AST, and gamma-glutamyl transferase, are routinely monitored in clinical trials. In Study 1603 Phase 3, mean increases in these PD markers were above baseline at Week 100, the last on-treatment visit in the study, and returned to baseline at Week 104, four weeks after stopping study drug.

FDA comment: It is not expected that the time-course of other PD markers will be the same as eGFR. Moreover, the purported mechanism of action is more consistent with a delay in the change in eGFR relative to bardoxolone concentration rather than a change in eGFR that is directly proportional to and immediately follows changes in measured bardoxolone concentration, as the Applicant asserts.

The justification provided by the Applicant for the adequacy of the 4-week washout in patients with AS is not compelling, and there is therefore uncertainty about the adequacy of the 4-week washout. To address this uncertainty, we developed a separate PK/PD model to characterize the washout (Appendix 6.5) of the reversible PD effect observed with bardoxolone to support the interpretation of the key secondary endpoint of CARDINAL Phase 3.

6.5. Technical Report for Pharmacokinetic/Pharmacodynamic Model

6.5.1. Objectives

- To develop a fit-for-purpose PK/PD model to describe the disease progression and drug effect of bardoxolone in patients with CKD due to AS and T2D
- To characterize the PD half-life and time to washout of the reversible PD effect of bardoxolone

6.5.2. Methods

6.5.2.1. Data

CARDINAL Phase 3 had limited off-treatment eGFR data (one measurement following the 4-week washout after Year 1 and Year 2). Data from Study RTA 402-005 (TSUBAKI) in patients with CKD and T2D were included in model development because TSUBAKI was the only trial in the development program with serial off-treatment collection of eGFR for up to 12 weeks post-dose.

Data from CARDINAL Phase 2 in patients with AS, as well as from Study 1102 in patients with CKD and T2D, were used for external validation of the model.

6.5.2.2. Model Development

6.5.2.2.1. Population PK Model

The Applicant's optimized PopPK model was used to obtain individual patient exposure metrics. The dataset used for the PopPK model was used as the source data for the derivation of daily average concentration (C_{avg}). During data preparation, it was discovered that the PopPK dataset was missing dosing records, most notably during Year 2 for CARDINAL Phase 3. To address this, the missing dosing records from the study datasets submitted by the Applicant (i.e., records from the exposure [EX] datasets) were inserted into the PopPK dataset and all covariate columns in the PopPK model were updated in the final dataset using last observation carried forward for the covariate. The measurements from the primary analysis were used as the source of eGFR measurements, and UACR at baseline and age were added as additional columns. This complete dataset was used for modeling analysis conducted by the review team.

6.5.2.2.2. Disease and Drug Effect Model

The process of describing eGFR changes over time was modelled using an indirect-response model (Dayneka et al. 1993) as follows:

$$\frac{deGFR}{dt} = K_{in} - eGFR * K_{out}(t)$$

where the change in the observed eGFR over time (*d*eGFR/*d*t) is controlled by a zero-order process parameterized as an apparent increase rate constant (K_{in}) and first order elimination process (K_{out}).

Disease status at baseline was described by the ratio between K_{in} and K_{out}. Disease progression was modeled as an exponential decline in the baseline status as follows:

$$DP = \frac{K_{in}}{K_{out}} = eGFR_{base} * e^{-k_{prog}*t}$$

where $eGFR_{base}$ is the eGFR at the start of a clinical trial and k_{prog} is the progression rate (Musuamba et al. 2015). A linear decline in baseline status was also tested during model development. Because of limited data to support disease progression in TSUBAKI, disease progression was only modelled for patients with AS.

The drug effect (DE) of bardoxolone was modeled using a nonlinear E_{max} function, in which the maximal effect of stimulation (S_{max}) or maximal effect of inhibition (I_{max}) is proportional to the potency parameter (half-maximal stimulatory concentration [SC_{50}] or half-maximal inhibitory concentration [IC_{50}]) and A is the drug exposure measure. The exposure measure selected was daily C_{avg} because the observed data suggests a potential lag time between changes in eGFR (Figure 11) and bardoxolone concentrations, leading to the conclusion that daily fluctuations in bardoxolone PK are unlikely to impact the observed eGFR changes. A sensitivity analysis to this assumption was conducted using individual concentration predictions from the Applicant's optimized PopPK model. Because there are limited data across a wide exposure range, SC_{50} will be expressed relative to S_{max} in the drug effect model:

$$DE = \frac{A * Smax}{A + SC_{50}}$$

Four different models were tested with drug effects incorporated either additively or multiplicatively on K_{in} or on K_{out}. Examples are shown below for incorporation on K_{in}.

$$Kin = TVk_{in} + DE$$

$$Kin = TVk_{in} * (1 + DE)$$

where TVK_{in} is the typical value of K_{in} in the absence of drug effects.

The model parameter K_{out} is the first-order rate constant for loss of eGFR over time and can be computed according to the following equation. The PD half-life can be derived from K_{out}.

$$K_{out}(t) = \frac{K_{in}}{eGFR_{base} * e^{-kprog*t}}$$

$$\text{PD half-life} = \frac{ln(2)}{Kout}$$

6.5.2.2.3. Inter-Individual and Residual Error Model

Exponential models were explored initially for inter-individual variability (IIV) in model parameters (i.e., $S_{max} = TV_{Smax} * e^{\eta Smax}$). The distribution of η (referred to as ETA) was assumed to be normally distributed with zero mean, and the variance was estimated as part of the model. If the distribution of the ETAs was not normal, then proportional IIV or transformations would be considered (e.g., the Manly transform):

$$ET1 = \frac{e^{\eta_{1*\gamma}} - 1}{\gamma}$$

The covariance between different parameters could also be assessed using additional random effects terms using the OMEGA BLOCK() option in NONMEM. ETA terms were only maintained in the model when they improved the fitting as assessed by comparing NONMEM objective function values with and without the inclusion of random effects along with consideration of the variance of the ETA.

The residual error model was a combination of additive and proportional error models, but other error models could also be explored.

$$Y = IPRED\ x\left(1 + \varepsilon_{prop}\right) + \ \varepsilon_{add}$$

where Y and IPRED represent the observed and individual predicted eGFR values, respectively. E_{add} and ε_{prop} are the additive and the proportional error terms on eGFR values, respectively. The distribution of ε was assumed to be normally distributed with mean zero. The variance (σ^2) terms were estimated as part of the population-model-fitting process.

The model was developed using R 3.6.1 (R Foundation for Statistical Computing, Austria), Piraña 2.9.9 (Pirana Software & Consulting BV), Perl-speaks-NONMEM (PsN) 5.0.0 (Department of Pharmaceutical Bioscience, Uppsala University, Sweden), and NONMEM 7.4.3 (ICON Development Solutions, USA) with Gfortran 4.6.0 (GNU compiler collection).

6.5.2.2.4. Model Selection

Structural model selection was based on model convergence, objective function value (OFV), condition number, and model goodness-of-fit. The specific goodness-of-fit plots used for consideration include concordance plot (observed value versus individual or population level prediction), residual-based diagnostics (e.g., individually weighted or conditionally weighted residuals), parameter or Empirical Bayes Estimate-based diagnostics and simulation-based diagnostics (e.g., prediction-corrected visual predictive checks). For models that were not nested, the Akaike Information Criterion (AIC) was used instead of OFV (Byon et al. 2013).

6.5.2.2.5. Covariate Model

A limited covariate evaluation was conducted on four covariates on model parameters: age, UACR, treatment, and disease population. All covariates were explored as dichotomized variables (i.e., age <30 years versus age ≥30 years or UACR ≤300 mg/g versus >300 mg/g, treatment group (bardoxolone or placebo) or disease population (AS versus T2D CKD). The choice of the value for dichotomization was based on the PK/PD model developed by the Applicant (age) or threshold for change in dosing regimen (UACR). Slowing of disease progression by drug was evaluated by inclusion of a treatment group (bardoxolone versus placebo) on disease progression slope.

6.5.2.2.6. Final Model Evaluation

Simulations were used to internally validate the final model. To that end, 500 simulations were generated using PsN to generate prediction-corrected visual predictive checks. Further model evaluation and quantification of parameter uncertainty was done using sampling importance resampling (Dosne et al. 2017).

6.5.2.2.7. Sensitivity Analyses

Three sensitivity analyses were conducted. Model diagnostics were compared when the final model was used on the dataset with individual predicted bardoxolone concentrations instead of C_{avg}, or when the

dataset only contained the CARDINAL Phase 3 trial (i.e., excluded TSUBAKI trial). The final model was also compared with the Applicant's exposure-response model.

6.5.2.2.8. External Validation of Final Model

The final model was used to simulate the time-course of change from baseline in eGFR in CARDINAL Phase 2 and Study 1103, which were not used during model development. A visual predictive check was used to compare model simulated versus observed eGFR values.

6.5.3. Results

6.5.3.1. Base Model Development

The indirect-response model with a proportional S_{max} on K_{in} and disease progression expressed as an exponential decline was the drug model with the lowest OFV (D1; Table 15). Inclusion of IIV on K_{in} or SC_{50} resulted in a large associated variance (ω^2_{SC50}: 2.13; ω^2_{Kin}: 3.97), and models with IIV on K_{in} and SC_{50} were therefore not considered further. In contrast, inclusion of IIV on S_{max} resulted in an acceptable variance (ω^2_{Smax}: 0.64) and a drop in OFV (I1: ΔOFV: -784.6). Inspection of the distribution of ETAs on S_{max} revealed a non-normal distribution and a proportional ETA was therefore explored (i.e., $S_{max} = TV_{SMAX} * (1 + ETA_{SMAX})$). Change in ETA structure for S_{max} resulted in a decrease in OFV (I4: ΔOFV: -58.4), normally distributed ETAs, and a decrease in variance for S_{max}. No correlation between ETAs for S_{max} and K_{prog} were observed, and the resulting IIV structure was therefore not changed further. Lastly, no indication of misspecification in residual error was observed (i.e., no deviation over time in [individually weighted residual] with respect to time) or deviation from normality of residuals and no further exploration of residual error structure was conducted. Model I4 was considered the final base model.

Table 15. Model Run Summary

ID	Description	Comments	OFV	ΔOFV (REF)
D1	K_{in}, S_{max} proportional		19836.3	
D2	K_{in}, S_{max} additive	Low precision on S_{max} (RSE: 434%)	19836.3	
D3	K_{out}, I_{max} proportional		20109.0	
D4	K_{out}, I_{max} additive		22051.0	
B1	+ Linear baseline		19920.5	+57.2 (D1)
I1	+ IIV S_{max}		19078.7	-784.6 (D1)
I2	+ IIV SC_{50}	High variance on IIV (2.13)	19017.2	-846.1 (D1)
I3	+ IIV K_{in}	High variance on IIV (3.97)	19279.0	-584.3 (D1)
I4	+ Proportional ETA S_{max}		19020.3	-58.4 (I1)

Source: Reviewer's analysis
Abbreviations: ETA, distribution of η; I_{max}, maximum inhibition; IIV, inter-individual variability; K_{in}, apparent increase rate constant; K_{out}, first order elimination rate constant; OFV, objective function value; RSE, relative standard error; S_{max}, maximal stimulatory factor; SC_{50}, potency parameter

6.5.3.2. Covariates and Model Refinement

The impact of age (<30 versus ≥ 30 years), UACR at baseline (≤300 mg/g versus >300 mg/g), disease population (AS versus non-AS), and treatment group were evaluated on S_{max} and K_{prog} as appropriate and are summarized in Table 16.

In univariate analysis, the inclusion of UACR on K_{prog} resulted in the largest significant drop in OFV and variance on K_{prog} (C1: ΔOFV: -39.1). While inclusion of age resulted in a drop in OFV (C2: ΔOFV: -13.5), the inclusion of age in addition to UACR resulted in a minimal drop in OFV (C4: ΔOFV: -4.1) and was

associated with low precision on the interaction term (relative standard error [RSE]: 49%). Inclusion of treatment group on K_{prog}, i.e., testing for interaction between treatment group and difference in rate of decline in kidney function, did not lower the OFV significantly (C3: ΔOFV: -2.9) and was associated with low precision (RSE: 60%); therefore, it was not considered in subsequent models. Notably, the estimate of the interaction between decline in disease progression and treatment group suggested a numerically steeper decline for bardoxolone-treated patients. Therefore, the only interaction on K_{prog} retained in subsequent models was UACR. Inspection of the distribution of ETA revealed a non-normal distribution for the ETA associated with K_{prog}, and a proportional ETA was therefore considered, which resulted in a drop in OFV (C5: ΔOFV: -7.3) and normal distribution of ETA.

Interaction between S_{max} and age (C6: ΔOFV: -2.5), and between UACR (C7: ΔOFV: -0.1) and disease population (C8: ΔOFV: -0.8) did not suggest that any of these covariates had a significant impact on S_{max}; therefore, model C5 was considered the final model.

Table 16. Exploration of Covariates

ID	Description	Comments	OFV	ΔOFV (REF)
C1	+K_{prog} UACR		18981.2	-39.1 (I4)
C2	+K_{prog} Age		19006.8	-13.5 (I4)
C3	+K_{prog} Treatment	Low precision on interaction (RSE 60%)	19017.4	-2.9 (I4)
C4	+K_{prog} Age	Low precision on Age/K_{prog} (RSE: 49%)	18977.1	-4.1 (C1)
C5	+K_{prog} ETA proportional		18973.8	-7.3 (C1)
C6	+Age S_{max}	Low precision on interaction (RSE: 56%)	18971.3	-2.5 (C5)
C7	+UACR S_{max}	Low precision on interaction (RSE: 313%)	18973.8	-0.1 (C5)
C8	+Disease population S_{max}	Low precision on interaction (RSE: 103%)	18973.1	-0.8 (C5)

Source: Reviewer's analysis
Abbreviations: ETA, distribution of η; I_{max}, maximum inhibition; K_{prog}, rate of disease progression; OFV, objective function value; RSE, relative standard error; S_{max}, maximal stimulatory factor; UACR, urinary albumin-to-creatinine ratio.

6.5.3.3. Evaluation of Final Model

A summary of the final parameter estimates, including the aforementioned covariates, is provided in Table 17. All model parameters were estimated with good precision (i.e., RSE <30%) and acceptable shrinkage on ETAs (i.e., shrinkage <35%).

Model diagnostics for the final model are shown in Figure 14. The model diagnostics show random scatter around the line of identity for PRED and IPRED versus the dependent variable (top row); no systematic trend between population prediction and time and conditionally weighted residuals (middle row); and constant variability and normally distributed residuals (bottom row). The distribution of post-hoc ETAs for both K_{prog} and S_{max} are normally distributed (Figure 15).

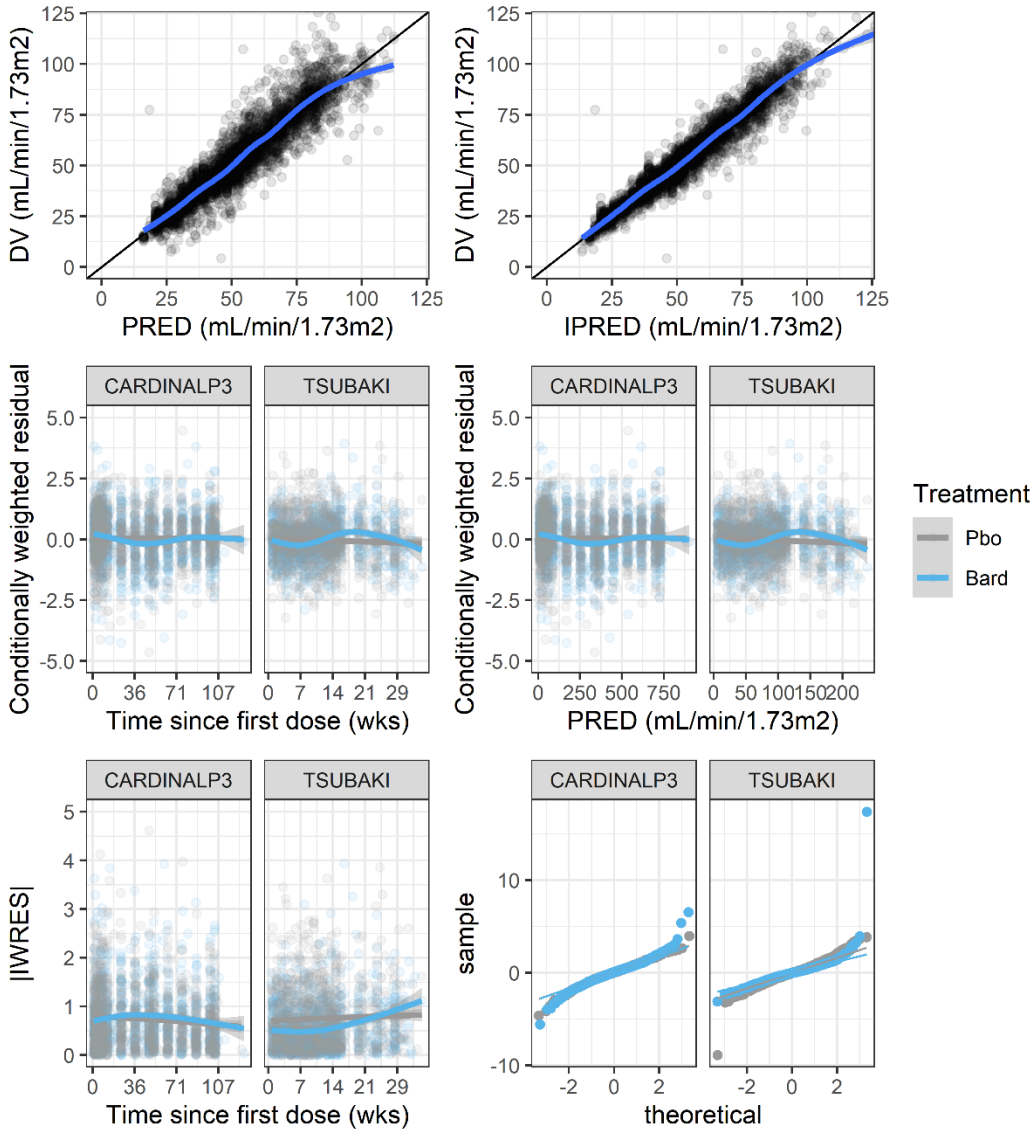
As shown by the visual predictive check in Figure 16, most of the observed data in the validation subset of data were distributed within the 5th and 95th percentiles of the prediction intervals. Similar predictive performance was observed when the eGFR profiles were split by study/treatment and UACR.

Table 17. Final Model Parameter Estimates

Parameter	Estimate	RSE (%)	Shrinkage (%)	SIR (95% CI)	SIR RSE (%)
Fixed effects					
S_{max} (*)	0.28	8.9	-	0.29 (0.24 to 0.35)	8
SC_{50} (ng/mL)	1.60	14.1	-	1.61 (1.05 to 2.42)	10
K_{in}[a] (mL/min/1.73m^2 per day)	2.28	26.9	-	2.28 (1.89 to 2.81)	12
$K_{prog,\ UACR \leq 300\ mg/g}$ (1/year)	0.04	3.9	-	0.04 (0.03 to 0.05)	4
$K_{prog,\ UACR > 300\ mg/g}$ (1/year)	0.20	11.2[a]	-	0.20 (0.15 to 0.25)	8[a]
IIV					
S_{max}[b] (CV%)	87%	18.2	33.8	87% (71% to 112%)	20
K_{prog}[b] (CV%)	184%	23.3	32.7	186% (127% to 333%)	27
RUV					
$\sigma_{Additive}$ (mL/min/1.73 m^2)	3.09	22.7	3	3.09 (2.89 to 3.3)	3
Proportional[c] (CV%)	7.69%	10.6	-	7.7% (7.3% to 8%)	2

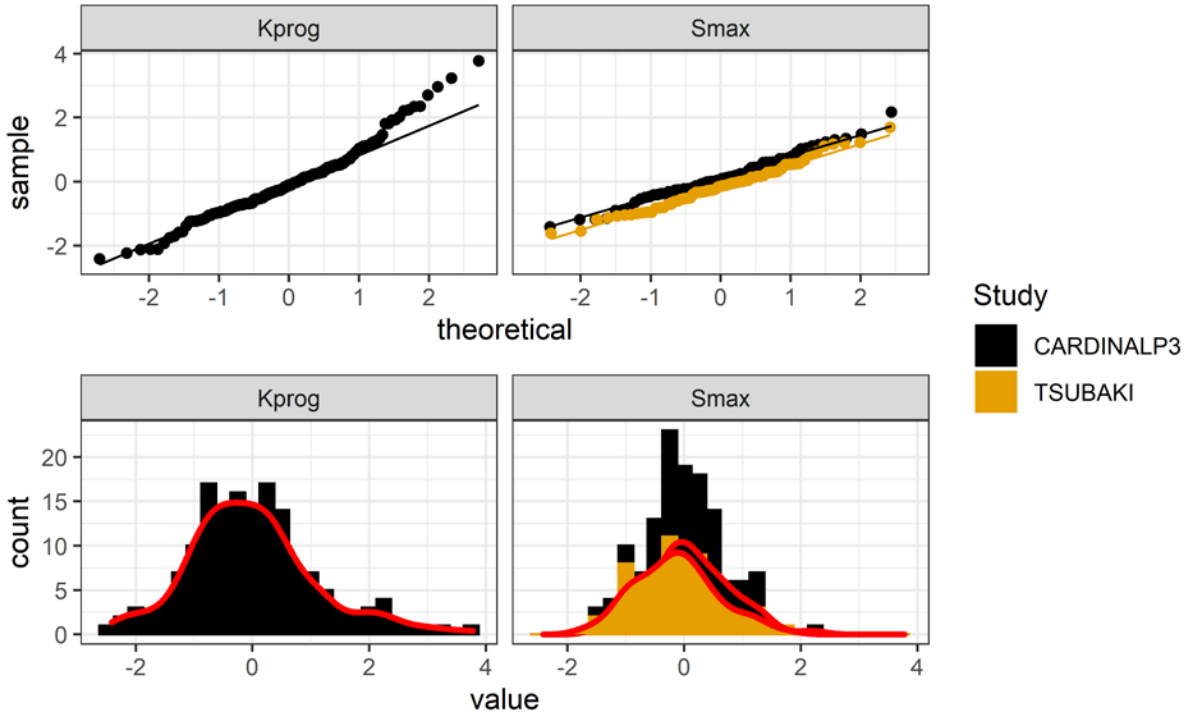
Source: Reviewer's analysis
[a] RSE for K_{prog} and UACR interaction
[b] sqrt(exp(ω^2)-1) * 100%
[c] θ * 100%
Abbreviations: CV, coefficient of variation; IIV, inter-individual variability; K_{in}, apparent increase rate constant; K_{prog}, rate of disease progression; RSE, relative standard error; RUV, residual variability; SIR, sampling importance resampling; S_{max}, maximal stimulatory factor; SC_{50}, potency parameter; UACR, urinary albumin-to-creatinine ratio.

Figure 14. Basic Goodness-of-Fit Plots for the Final Model.



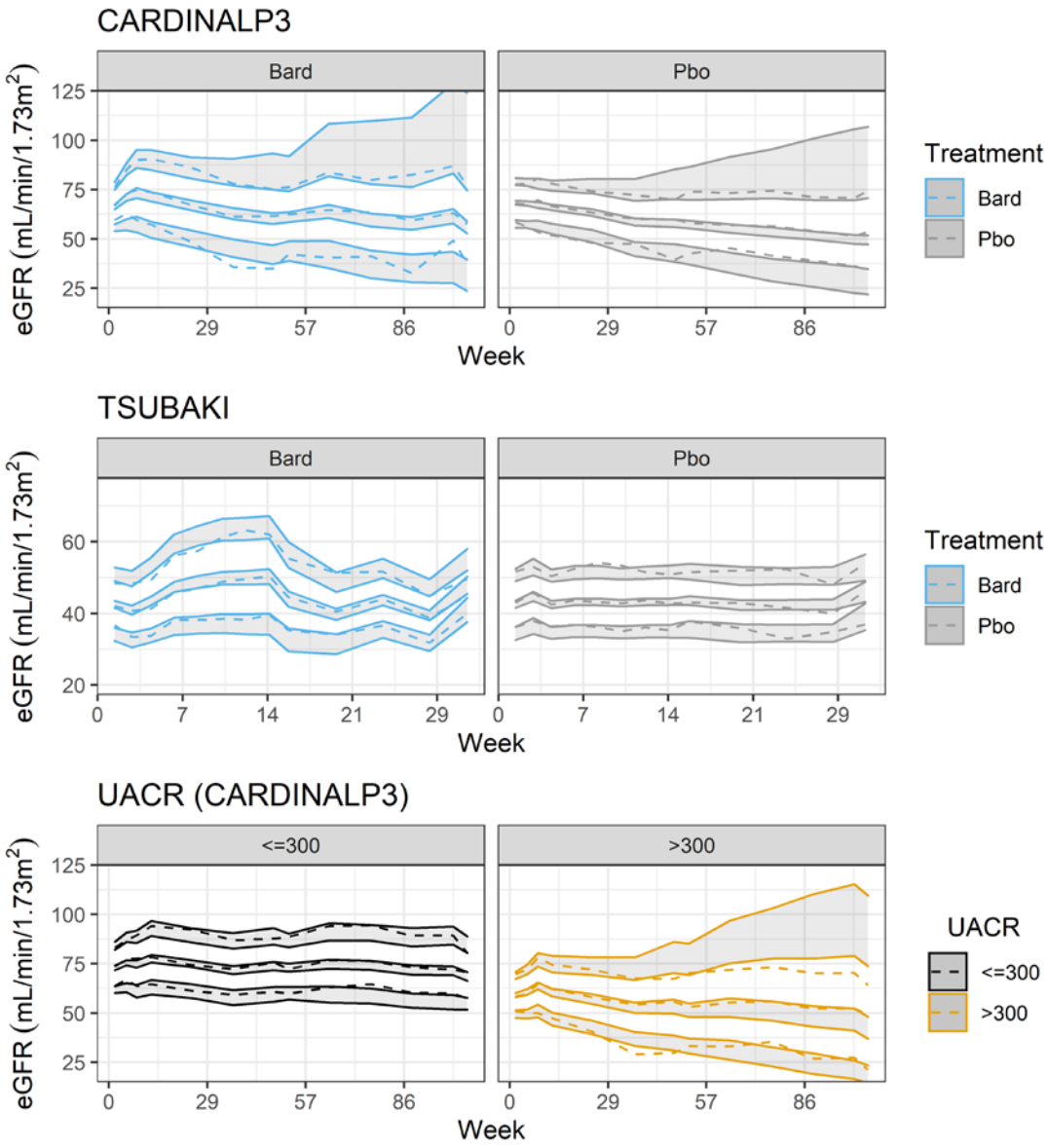
Source: Reviewer's analysis
Goodness-of-fit plots for final model. Blue and gray shaded lines represented smoothed regression through the data.
Abbreviations: Bard, bardoxolone; DV, dependent variable; Pbo, placebo; PRED, population prediction; IPRED, individual prediction; IWRES, individually weighted residual.

Figure 15. ETA Distribution Plot



Source: Reviewer's analysis
Goodness-of-fit plots for ETA distr bution of disease progression (K_{prog}) and maximum drug effect (S_{max}) by study, represented as a quantile-quantile plot (top panel) and histogram / smoothed density estimate in red (bottom panel).
Abbreviations: ETA, distr bution of η; K_{prog}, rate of disease progression; S_{max}, maximal stimulatory factor.

Figure 16. Visual Predictive Checks for PK/PD Model



Source: Reviewer's analysis
Visual predictive checks stratified by (top) CARDINAL P3 (left panel: bardoxolone, right panel: placebo), (middle) TSUBAKI (left panel: bardoxolone, right panel: placebo), (bottom) baseline UACR for CARDINAL P3 (left panel: ≤300 mg/g, right panel: >300 mg/g). Dashed lines: observed data shown as 5th, 50th, and 95th quantiles. Solid lines and gray shading represent the 5th, 50th, and 95th prediction intervals. CARDINAL P3 excludes three observations past 110 weeks after the last dose (last analysis visit is Week 104)
Abbreviations: eGFR, estimated glomerular filtration rate; Pbo, placebo; PD, pharmacodynamics; PK, pharmacokinetics; UACR, urinary albumin-to-creatinine ratio.

6.5.3.4. Sensitivity Analysis

6.5.3.4.1. Exposure Metric

Similar parameter estimates were obtained when using predicted bardoxolone concentration at the time of eGFR measurement instead of daily average bardoxolone concentration when fitting the final model structure to CARDINAL Phase 3. This is likely because of the difference in time-scale of changes in

eGFR relative to bardoxolone concentration, such that daily fluctuations have a lesser impact on the change in eGFR, therefore supporting the selection of C_{avg} as the exposure measure to describe changes in eGFR.

6.5.3.4.2. Impact by Study

Minimal impact of the inclusion of TSUBAKI on the model parameters were observed except for K_{in} (Table 18). This difference suggests that there might be an interaction between disease population and K_{in}. During model exploration, an IIV on K_{in} was explored but there was insufficient data to support the inclusion of the term. Inclusion of an interaction between disease population reduced OFV (ΔOFV: -27.3), but with low precision on the interaction term (RSE: 47%).

Table 18. Impact of Inclusion of TSUBAKI on Model Parameters

	With TSUBAKI			Without TSUBAKI		
Parameter	**Estimate**	**RSE (%)**	**Shrinkage (%)**	**Estimate**	**RSE (%)**	**Shrinkage (%)**
Fixed effects						
S_{max} (*)	0.28	8.9	-	0.31	11.4	-
SC_{50} (ng/mL)	1.60	14.1	-	1.54	20.4	-
K_{in} (mL/min/1.73m^2 per day)	2.28	26.9	-	3.03	33.4	-
$K_{prog,\ UACR \leq 300\ mg/g}$ (1/year)	0.04	3.9	-	0.04	4.2	-
$K_{prog,\ UACR > 300\ mg/g}$ (1/year)	0.20	11.2[a]	-	0.20	10.8[a]	-
IIV						
S_{max} [b] (CV%)	87%	18.2	33.8	69%	23.7	36.8
K_{prog} [b] (CV%)	184%	23.3	32.7	205%	26.2	9.2
RUV						
$\sigma_{Additive}$ (mL/min/1.73 m^2)	3.09	22.7	3	2.17	19.2	4
Proportional[c] (CV%)	7.69%	10.6	-	8.9%	5.5	-

Source: Reviewer's analysis
[a] RSE for K_{prog} and UACR interaction
[b] sqrt(exp(ω^2)-1) * 100%
[c] θ * 100%

Abbreviations: CV, coefficient of variation; IIV, inter-individual variability; K_{in}, apparent increase rate constant; K_{prog}, rate of disease progression; RSE, relative standard error; RUV, residual variability; SC_{50}, potency parameter; S_{max}, maximal stimulatory factor; UACR, urinary albumin-to-creatinine ratio.

6.5.3.4.3. Comparison to Applicant's Model

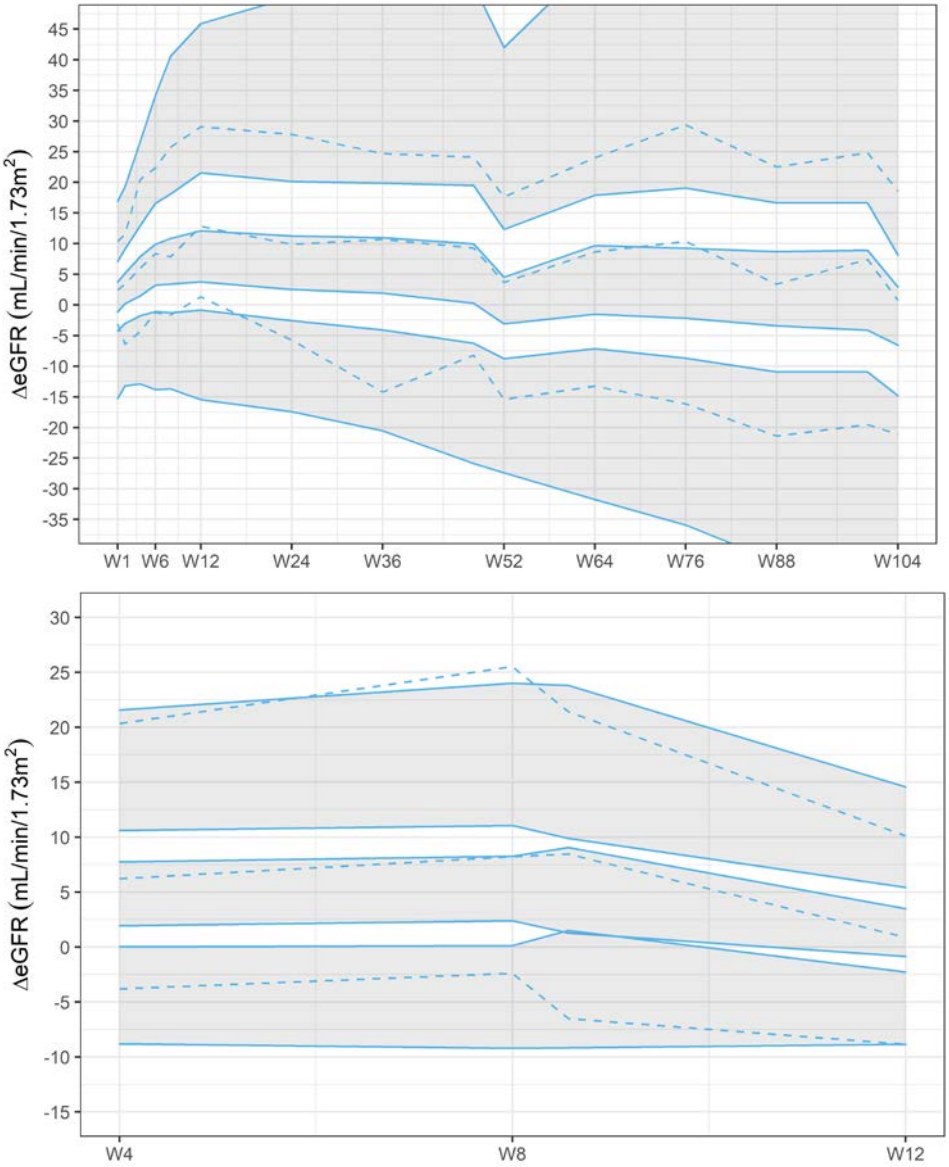
The indirect response model has a lower AIC compared to the direct response model developed by the Applicant (ΔAIC: -141.4). The difference is likely due to the Applicant's model over predicting the onset of change (i.e., the time-course during the first 6 weeks) in eGFR (Figure 13).

6.5.3.5. Model Validation

Data from CARDINAL Phase 2 in patients with AS and Study 1102 in patients with T2D, which were not included in the model development, were used as an external validation of the model. For this external validation, the 500 datasets were simulated by the model using the dosing records and predicted PK in CARDINAL Phase 2 and Study 1102, respectively. Figure 17 shows that the model captures the time-course of observed eGFR. A comparison of the observed and model-predicted eGFR values during washout are shown in Table 19. Figure 18 shows observed and model predicted eGFR in CARDINAL Phase 3 and beyond the last analysis visit at week 104. This figure shows that the model (solid line and shaded area) captures the time-course of the observed eGFR (error bars) well but under-predicts the

early peak increase. The figure shows that the model predicts that the reversible PD effect on eGFR observed with bardoxolone has mostly resolved around Week 110.

Figure 17. External Validation



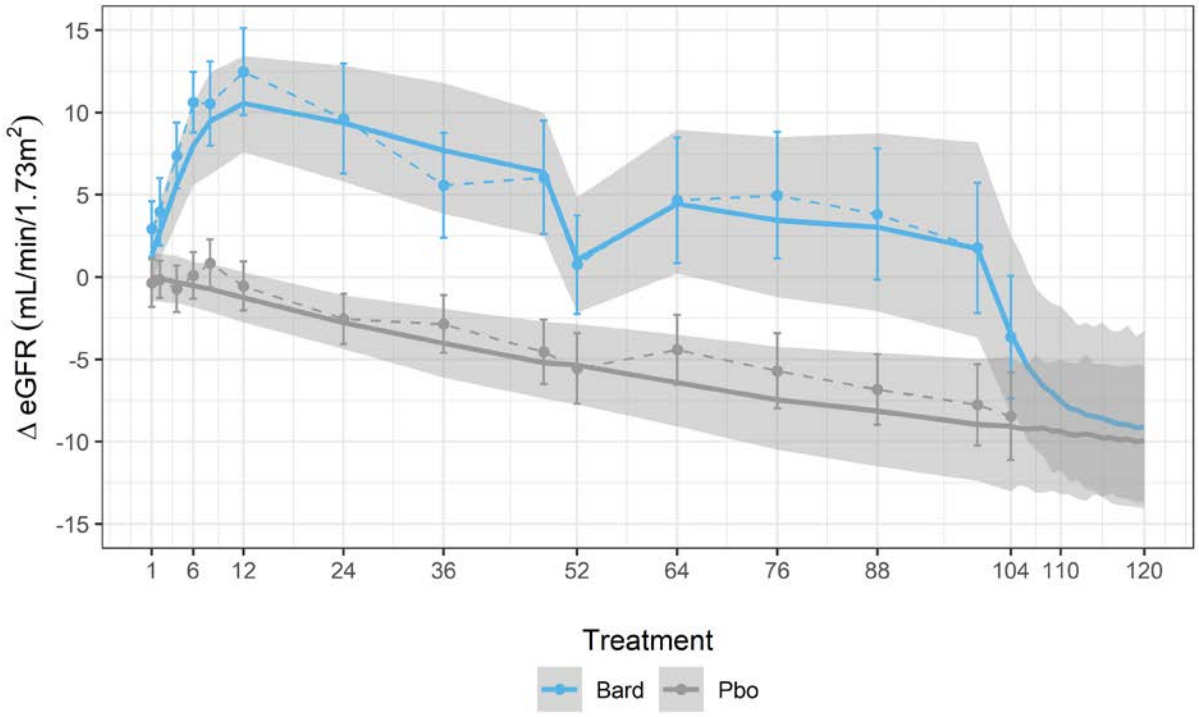
Source: Reviewer's analysis
Model-predicted eGFR values with bardoxolone treatment for CARDINAL Phase 2 (top panel) and Study 402-C-1102 (bottom panel). Dashed lines: observed data shown as 5th, 50th, and 95th quantiles. Solid lines and gray shading represent the 5th, 50th, and 95th prediction intervals.
Abbreviations: eGFR, estimated glomerular filtration; W, week.

Table 19. Observed vs. Model-Predicted Change in Baseline eGFR During Washout for Bardoxolone

	eGFR (mL/min/1.73m^2) Change From Baseline Mean (95% CI)	
Study Visit	**Observed**	**Predicted**
CARDINAL Phase 3		
Week 52 (Year 1)	0.8 (-2.2 to 3.7)	0.9 (-1.9 to 4.2)
Week 104 (Year 2)	-3.6 (-7.4 to 0.1)	-3.4 (-8.3 to 2.7)
TSUBAKI		
Week 4	3.1 (1.8 to 4.3)	2.7 (1.4 to 4.1)
Week 8	0.5 (-0.8 to 1.8)	0.8 (-0.5 to 1.9)
Study 402-C-1102		
Week 4	0.5 (-1.9 to 3.0)	1.5 (-0.3 to 3.5)
CARDINAL Phase 2		
Week 52 (Year 1)	1.5 (-2.7 to 5.7)	1.6 (-2.5 to 5.4)
Week 104 (Year 2)	-1.1 (-6.5 to 4.2)	-2.1 (-7.8 to 4.7)

Source: Reviewer's analysis
Abbreviations: eGFR, estimated glomerular filtration.

Figure 18. Observed and Predicted Time-Course in eGFR With a Predicted Longer Washout Period in CARDINAL Phase 3.



Source: Reviewer's analysis
Dashed line and error bars represent the observed eGFR data in CARDINAL Phase 3 (mean ± 95% confidence interval). Solid lines and shaded area represent model-predicted values (mean ± 95% confidence interval).
Abbreviations: Bard, bardoxolone; eGFR, estimated glomerular filtration; Pbo, placebo.

6.5.3.6. Pharmacodynamic Half-Life

The PK/PD model parameters can be used to compute the half-life of the reversible PD effect on eGFR (Table 20). The PD half-life can also be used to estimate the percentage of the reversible PD effect on eGFR that remains at 4 and 8 weeks after the last dose in clinical trials. For CARDINAL Phase 3, it is

predicted that 21 to 38% of the PD effect would remain after a 4-week washout, supporting that the washout was not of sufficient duration.

Table 20. Model-Predicted Resolution of Reversible PD Effect in CARDINAL Phase 3; Study 402-C-1102 and TSUBAKI

Study Visit	PD Half-Life Days (95% CI)	% PD Effect Remaining (95% CI) Week 4	Week 8
CARDINAL Phase 3			
Week 48	17 (14 to 20)	32 (25 to 39)	10 (6 to 15)
Week 100	15 (12 to 18)	28 (21 to 35)	8 (4 to 12)
Study 402-C-1102			
Week 8	9 (7 to 11)	11 (7 to 16)	1 (0 to 3)
TSUBAKI			
Week 16	12 (10 to 15)	20 (14 to 26)	4 (2 to 7)

Source: Reviewer's analysis
Abbreviations: PD, pharmacodynamics.

6.5.4. Conclusions

The FDA developed a PK/PD model to explore the adequacy of the washout period in CARDINAL Phase 3. Parameterization of the model assumed that eGFR can be described as a balance between the apparent rate of increase in eGFR (K_{in}), modeled as a zero-order input, and the apparent rate of eGFR decrease described as a first-order elimination (K_{out}). In this model, the baseline eGFR is the ratio between the apparent rate of increase and decrease in eGFR (i.e., K_{in}/K_{out}). The ratio of the apparent rate of increase and decrease in eGFR was time-varying to allow for the baseline eGFR to decrease over time to describe the disease progression. The effect of bardoxolone was described using an E_{max} model, which stimulated the apparent rate of increase in eGFR leading to an increase in eGFR which will be reversed after stopping treatment. All model parameters were estimated with good precision (i.e., <30%) and the shrinkage on ETAs was acceptable (i.e., <35%) indicating that there was sufficient data to inform estimating S_{max} and K_{prog} values for each patient. Model diagnostics and external validation confirmed that the model adequately describes the time-course of eGFR in patients with AS.

The objective of this model was to estimate time of washout of the reversible PD effect on eGFR after treatment with bardoxolone has stopped. Pharmacodynamic half-life is influenced by baseline eGFR and UACR, therefore, studies that enroll patients with less severe kidney disease, as measured by higher baseline eGFR values and UACR <300 mg/g, will require a longer washout. In AS, the PD half-life is 15 days after 2 years of treatment with bardoxolone. It will take approximately four half-lives or 60 days to wash out over 90% of the reversible PD effect. The PD half-life is shorter for CKD in T2D. The PD half-life was 9 days in Study 1102 when bardoxolone was given for 8 weeks, and 12 days in TSUBAKI when bardoxolone was given for 16 weeks. Therefore, a 4-week washout is appropriate for studies with treatment duration ≤ 8 weeks in patients with Stage 3-4 CKD (Appendix 6.4, Applicant's Justification number 3).

The design of CARDINAL Phase 3 with a 4-week washout does not allow for the evaluation of the potential of bardoxolone to slow disease progression. The eGFR values collected 4 weeks after treatment cessation at Week 52 or Week 104 still represent the reversible PD effect of bardoxolone based on the PK/PD model developed by the FDA and the exposure-response model developed by the

Applicant, and neither model suggests that bardoxolone slows the progression of decline in kidney function.

6.6. Technical Details in the Efficacy Analysis

6.6.1. Multiple Imputation in the Off-Treatment Analysis at Week 104

The analyses of off-treatment change from baseline in eGFR at Week 52 and Week 104 were pre-specified to use ANCOVA and missing values were to be imputed using multiple imputation based on the assigned treatment group. The multiple imputation procedure accounts for uncertainty in predicting missing values by including variability into the multiple imputed values. By creating multiple completed datasets with all missing values imputed, each imputed dataset is fitted with the same statistical model to obtain estimates of treatment effect, and results are then combined to provide an overall estimate with standard error accounting for the variability between imputed datasets.

The multiple imputation procedure needs to model the distribution of missing values, and the validity of results depends on statistical modeling. The SAP Version 3.0 did not specify which factors were to be included in the imputation step. For the primary endpoint analyses, the Applicant included three factors in the imputation procedure for the Year-1 analysis, but only two factors for the Year-2 analysis.

- For Week 52, the multiple imputations step included baseline eGFR, randomized UACR strata and fraction of 1-year exposure to treatment (TR01DUR).
- For Week 104, the multiple imputations step included baseline eGFR and randomized UACR strata.

The reason to exclude the fraction of 2-year exposure to treatment (TR02DUR) in the Week 104 analysis was not stated in the final clinical study report. As shown in Table 21, the placebo-corrected difference in the off-treatment change from baseline in eGFR at Week 104 is no longer statistically significant when TR02DUR is included in the multiple imputation step.

Table 21. Analyses of Off-Treatment Change from Baseline in eGFR With or Without Treatment Exposure

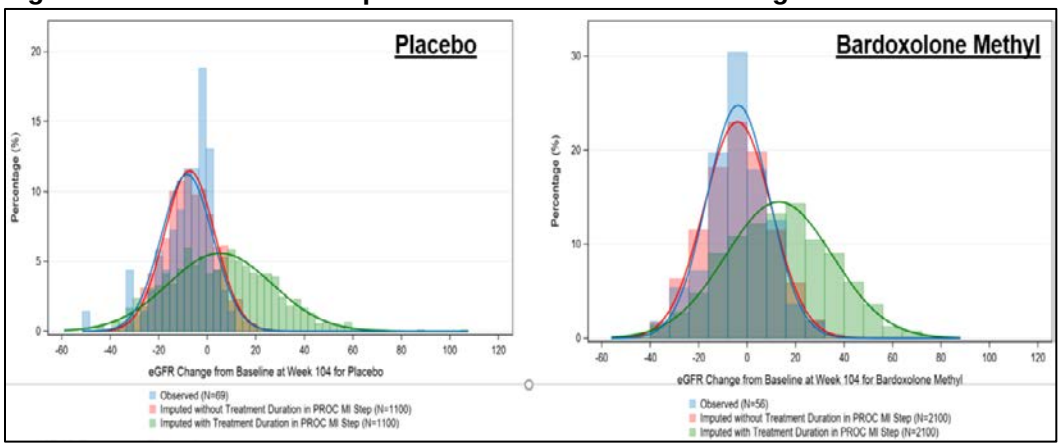
Imputation Approach	Placebo	Bardoxolone	Difference	P-value
Week 52 LS Mean (SE)				
Proc MI with TR01DUR	-6.1 (1.24)	-1.0 (1.25)	5.1 (1.66)	0.0021
Proc MI without TR01DUR	-6.2 (1.20)	-0.8 (1.22)	5.4 (1.65)	0.0012
Week 104 LS Mean (SE)				
Proc MI with TR02DUR	-7.7 (3.37)	-3.2 (3.55)	4.5 (4.65)	0.3365
Proc MI without TR02DUR	-10.7 (1.40)	-6.5 (1.46)	4.3 (1.88)	0.0232

Source: Applicant's analysis, verified by the reviewer
Abbreviations: eGFR, estimated glomerular filtration rate; LS, least squares, SE, standard error.

The Applicant argued that imputation including TR02DUR produced a range of eGFR values that disproportionally fall outside the range of observed values (for over 30% of imputed values) and lead to a standard error of the estimated treatment difference that is 2.4-times larger than with the observed Week 104 data. These anomalies did not occur when imputing missing Week 52 data, with only 3% of imputed values outside the observed range of values. Observed Week 104 change from baseline eGFR values range from -49.0 to +28.2 mL/min/1.73 m^2, while the maximum imputed change was +88.6 mL/min/1.73 m^2. The Applicant argued that the imputed values created when TR02DUR is included in the imputation step introduce change from baseline eGFR values that are not biologically

plausible. Figure 19 displays the distributions of observed and imputed eGFR change from baseline at Week 104.

Figure 19. Distribution of Imputed and Observed eGFR Change From Baseline at Week 104



Source: Applicant's figure
Placebo (left panel): Blue, observed (N=69); Red, imputed without treatment duration in PROC MI step (N=1100); Green, imputed with treatment duration in PROC MI step (N=1100)
Bardoxolone methyl (right panel): Blue, observed (N=56); Red, imputed without treatment duration in PROC MI step (N=2100); Green, imputed with treatment duration in PROC MI step (N=2100)
Abbreviations: eGFR, estimated glomerular filtration.

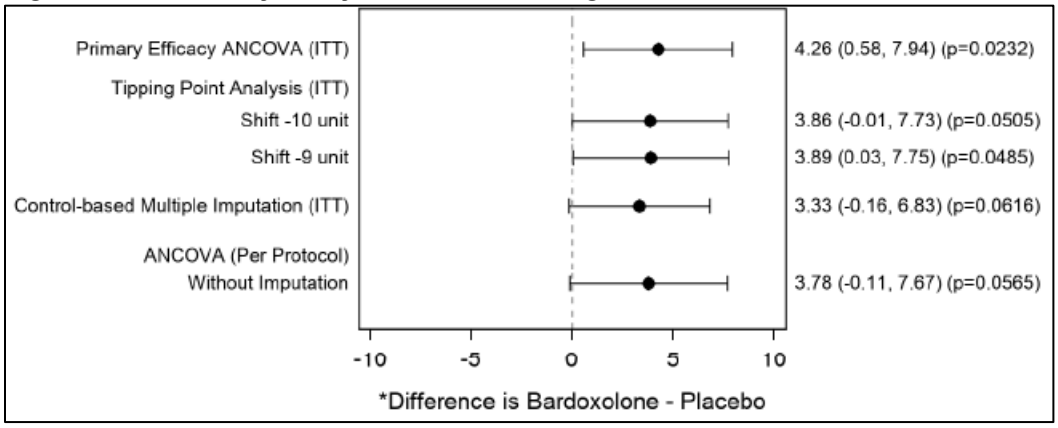
The Agency agrees with the Applicant's assessment regarding the deviations of the distributions of the imputed values from the observed range of eGFR values. However, it is also not reasonable to assume the imputed values should follow the range of the observed values closely. The Agency acknowledges the Applicant's explanation. Nevertheless, loss of statistical significance based on a change in a single factor in the analytic model raises concerns regarding the robustness of the study's findings.

6.6.2. Additional Sensitivity Analyses

Additional prespecified analyses were performed to assess the robustness of conclusions to the primary analysis of the Year-2 key secondary efficacy endpoint and to assess the assumption of missing at random. Sensitivity analyses, such as tipping point with multiple imputation, control-based multiple imputation, and the ANCOVA model fit to the per protocol population, are summarized in Figure 20.

In the tipping point analysis, patients in the bardoxolone group with a missing value were assigned a shift parameter in the imputation procedure for progressively worse values to find the point at which statistical significance is lost. The control-based multiple imputation sensitivity analysis imputes all missing Week 104 eGFR values with multiple imputation using the Week 104 data from the placebo group. The per-protocol population analysis is performed using the ANCOVA model without imputing the missing data.

Figure 20. Sensitivity Analyses of eGFR Change From Baseline to Week 104



Source: CSR Figure 7, verified by reviewer
Abbreviations: ANCOVA, analysis of covariance; eGFR, estimated glomerular filtration; ITT, intent-to-treat.

Results of prespecified sensitivity analyses:

- Tipping Point with Multiple Imputation: The tipping point for the Year-2 off-treatment result, where the treatment effect loses significance, is a shift of -10 mL/min/1.73 m^2 in the imputed off-treatment missing bardoxolone eGFR values at Week 104. In other words, eGFR values for each of the bardoxolone patients who did not contribute to the primary off-treatment analysis would be 10 mL/min/1.73 m^2 lower than the observed mean off-treatment eGFR in the bardoxolone group in order for the treatment effect to lose significance for a two-sided alpha of 0.05.
- Control-Based Imputation: This sensitivity analysis was performed to assess the impact of missing data using placebo (control)-based multiple imputation. The least squares (LS) mean change from baseline in eGFR at Week 104 was -11.0 mL/min/1.73 m^2 for the placebo group and -7.7 mL/min/1.73 m^2 for the bardoxolone group. The placebo-corrected LS mean difference of 3.3 did not achieve the statistical significance of 0.05 (nominal p = 0.062).
- Per-Protocol Population: The LS mean change from baseline in eGFR at Week 104 was -11.4 mL/min/1.73 m^2 for the placebo group and -7.6 mL/min/1.73 m^2 for the bardoxolone group. Treatment with bardoxolone did not show a significant higher mean change from baseline in eGFR relative to placebo at Week 104, with a placebo-corrected LS mean difference of 3.8 (nominal p = 0.057).

Although numerically in favor of bardoxolone, both the control-based analysis and per-protocol analyses just missed the nominal statistical significance level of 0.05.

6.7. Safety Analysis

6.7.1. Extent of Exposure

In CARDINAL Phase 3, the mean duration of study drug exposure was 22 months in both bardoxolone and placebo groups (Table 22). This represents an overall exposure of 121 patient-years for bardoxolone and 144 patient-years for placebo.

In BEACON, the mean duration of study drug exposure was 7.0 and 7.8 months for patients in the bardoxolone and placebo groups. This represents an overall exposure of 718 patient-years for bardoxolone and 790 for placebo.

Table 22. Duration of Exposure, Safety Population, CARDINAL Phase 3

Exposure	Bardoxolone N=77	Placebo N=80
Duration of treatment, months		
Mean (SD)	17.5 (7.9)	20.3 (5.1)
Median (min, max)	22.4 (0.5, 23.0)	22.4 (0.5, 22.8)
Patients treated, by duration, n (%)		
<1 month	1 (1.3)	1 (1.2)
≥1 month	76 (98.7)	79 (98.8)
≥3 months	67 (87.0)	79 (98.8)
≥6 months	64 (83.1)	78 (97.5)
≥12 months	58 (75.3)	69 (86.2)

Source: Reviewer's analysis
Abbreviations: SD, standard deviation.

6.7.2. Deaths and Serious Adverse Events

In CARDINAL Phase 3, there were no deaths or concerning imbalances in the pattern of SAEs in the bardoxolone-treated group (Table 23). There were seven SAEs related to acute kidney injury, proteinuria, CKD, or ESRD. Four of these were in the bardoxolone-treated group compared to three in the placebo group (Table 27). The SAE of "Hypertensive crisis" in the bardoxolone-treated group was in a patient that was being treated for hypertension and had been off lisinopril starting 2 weeks prior to the event. The investigator noted it was probable that the SAE was due to the patient being off of lisinopril.

Table 23. Serious Adverse Events,[a] Safety Population, CARDINAL Phase 3

SAE	Bardoxolone N=77 n (%)	Placebo N=80 n (%)	Absolute Risk Difference (95.0% CI)[b]
Primary System Organ Class Preferred Term			
Renal and urinary disorders	4 (5.2)	3 (3.8)	1.4 (-5.0, 7.9)
Acute kidney injury	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
End stage renal disease	2 (2.6)	2 (2.5)	0.1 (-4.8, 5.0)
Proteinuria	1 (1.3)	1 (1.2)	0.0 (-3.5, 3.6)
Respiratory, thoracic and mediastinal disorders	2 (2.6)	1 (1.2)	1.3 (-3.0, 5.7)
Pneumomediastinum	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Pneumothorax	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Asthma	0 (0.0)	1 (1.2)	-1.2 (-3.7, 1.2)
Metabolism and nutrition disorders	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Dehydration	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Vascular disorders	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Hypertensive crisis	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Injury, poisoning and procedural complications	1 (1.3)	2 (2.5)	-1.2 (-5.5, 3.1)
Clavicle fracture	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Rib fracture	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Scapula fracture	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Animal bite	0 (0.0)	1 (1.2)	-1.2 (-3.7, 1.2)
Laceration	0 (0.0)	1 (1.2)	-1.2 (-3.7, 1.2)

SAE	Bardoxolone N=77 n (%)	Placebo N=80 n (%)	Absolute Risk Difference (95.0% CI)[b]
Primary System Organ Class Preferred Term			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.3)	2 (2.5)	-1.2 (-5.5, 3.1)
Colon adenoma	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Carcinoid tumor	0 (0.0)	1 (1.2)	-1.2 (-3.7, 1.2)
Prostate cancer	0 (0.0)	1 (1.2)	-1.2 (-3.7, 1.2)
Immune system disorders	0 (0.0)	1 (1.2)	-1.2 (-3.7, 1.2)
Anaphylactic reaction	0 (0.0)	1 (1.2)	-1.2 (-3.7, 1.2)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (1.2)	-1.2 (-3.7, 1.2)
Osteoarthritis	0 (0.0)	1 (1.2)	-1.2 (-3.7, 1.2)
Reproductive system and breast disorders	0 (0.0)	1 (1.2)	-1.2 (-3.7, 1.2)
Ovarian mass	0 (0.0)	1 (1.2)	-1.2 (-3.7, 1.2)
General disorders and administration site conditions	0 (0.0)	2 (2.5)	-2.5 (-5.9, 0.9)
Non-cardiac chest pain	0 (0.0)	1 (1.2)	-1.2 (-3.7, 1.2)
Edema peripheral	0 (0.0)	1 (1.2)	-1.2 (-3.7, 1.2)
Infections and infestations	0 (0.0)	2 (2.5)	-2.5 (-5.9, 0.9)
Empyema	0 (0.0)	1 (1.2)	-1.2 (-3.7, 1.2)
Pneumonia	0 (0.0)	2 (2.5)	-2.5 (-5.9, 0.9)
Nervous system disorders	0 (0.0)	2 (2.5)	-2.5 (-5.9, 0.9)
Ischemic stroke	0 (0.0)	1 (1.2)	-1.2 (-3.7, 1.2)
Status migrainosus	0 (0.0)	1 (1.2)	-1.2 (-3.7, 1.2)

Source: Reviewer's analysis
[a] Treatment-emergent AEs defined as occurring within 30 days
[b] Difference is shown between Bardoxolone and Placebo
Abbreviations: SAE, serious adverse event.

6.7.3. Adverse Events Leading to Discontinuation

In CARDINAL Phase 3, there were more patients who discontinued treatment due to adverse events in the bardoxolone-treated group compared to placebo (Table 24). The most common adverse events associated with discontinuation of bardoxolone were increases in liver enzymes, BNP or NT-proBNP, muscle spasms and gastroesophageal reflux disease. Increase in BNP/NT-proBNP and transient increase in liver enzymes have been observed in multiple clinical trials, including BEACON. There were four patients who discontinued bardoxolone treatment due to acute kidney injury, proteinuria or CKD/ESRD compared to two in the placebo group (Table 27).

Table 24. FDA MedDRA Queries Leading to Discontinuation,[a] Safety Population, CARDINAL Phase 3

TEAE	Bardoxolone N=77 n (%)	Placebo N=80 n (%)	Absolute Risk Difference (95% CI)[c]
System Organ Class *FDA Medical Query (Broad)*[b] Preferred Term			
Patients with at least 1 AE leading to discontinuation	17 (22.1)	4 (5.0)	17.1 (6.7, 27.5)

TEAE	Bardoxolone N=77 n (%)	Placebo N=80 n (%)	Absolute Risk Difference (95% CI)[c]
System Organ Class			
FDA Medical Query (Broad)[b]			
Preferred Term			
Hepatobiliary disorders			
Hepatic injury	6 (7.8)	0 (0.0)	7.8 (1.8, 13.8)
Alanine aminotransferase increased	6 (7.8)	0 (0.0)	7.8 (1.8, 13.8)
Aspartate aminotransferase increased	3 (3.9)	0 (0.0)	3.9 (-0.4, 8.2)
Gamma-glutamyltransferase increased	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Renal and urinary disorders			
Acute kidney injury	3 (3.9)	0 (0.0)	3.9 (-0.4, 8.2)
Acute kidney injury	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Blood creatinine increased	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Glomerular filtration rate decreased	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Gastrointestinal disorders			
Dyspepsia	2 (2.6)	0 (0.0)	2.6 (-1.0, 6.2)
Gastroesophageal reflux disease	2 (2.6)	0 (0.0)	2.6 (-1.0, 6.2)
Musculoskeletal and connective tissue disorders			
Myalgia	2 (2.6)	0 (0.0)	2.6 (-1.0, 6.2)
Muscle spasms	2 (2.6)	0 (0.0)	2.6 (-1.0, 6.2)
Skin and subcutaneous tissue disorders			
Alopecia	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Alopecia	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Unknown			
Hypotension	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Dehydration	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
General disorders and administration site conditions			
Peripheral edema	1 (1.3)	1 (1.2)	0.0 (-3.5, 3.6)
Edema peripheral	1 (1.3)	1 (1.2)	0.0 (-3.5, 3.6)

Source: Reviewer's analysis
[a] Treatment-emergent AEs defined as occurring within 30 days
[b] Version 2020_01_29
[c] Difference is shown between Bardoxolone and Placebo
Abbreviations: AE, adverse event; CI, confidence interval.

6.7.4. Treatment-Emergent Adverse Events

A summary of treatment-emergent adverse events for CARDINAL Phase 3 is shown in Table 25 by system organ class and preferred term and in Table 26 by FDA MedDRA Queries, and for BEACON in Table 28 by system organ class and preferred term. Adverse events related to acute kidney injury, proteinuria and CKD/ESRD are summarized in Table 27. An imbalance in adverse events related to hyperkalemia was observed in CARDINAL Phase 3 and was associated with a greater incidence of elevated serum potassium levels (>5.5 mEq/L: 33% vs 19%; >6 mEq/L: 12% vs 4%; >6.5 mEq/L: 0 vs 1%). No imbalance was observed in BEACON related to hyperkalemia or serum potassium.

Table 25. Treatment-Emergent Adverse Events Occurring at 5% Higher Frequency in Treatment Arm Than Comparator Arm,[a] Phase 3 Safety Population, CARDINAL Phase 3

TEAE	Bardoxolone N=77 n (%)	Placebo N=80 n (%)	Absolute Risk Difference (95.0% CI)[b]
Primary System Organ Class Preferred Term			
Investigations	59 (76.6)	32 (40.0)	36.6 (22.3, 50.9)
Alanine aminotransferase increased	36 (46.8)	2 (2.5)	44.3 (32.6, 55.9)
Aspartate aminotransferase increased	19 (24.7)	1 (1.2)	23.4 (13.5, 33.4)
Weight decreased	10 (13.0)	1 (1.2)	11.7 (3.8, 19.6)
Brain natriuretic peptide increased	11 (14.3)	3 (3.8)	10.5 (1.7, 19.4)
Gastrointestinal disorders	41 (53.2)	29 (36.2)	17.0 (1.7, 32.3)
Diarrhea	12 (15.6)	6 (7.5)	8.1 (-1.9, 18.0)
Vomiting	7 (9.1)	3 (3.8)	5.3 (-2.3, 13.0)
Respiratory, thoracic and mediastinal disorders	25 (32.5)	17 (21.2)	11.2 (-2.6, 25.0)
Epistaxis	7 (9.1)	0 (0.0)	9.1 (2.7, 15.5)
Cough	8 (10.4)	3 (3.8)	6.6 (-1.3, 14.6)
Musculoskeletal and connective tissue disorders	48 (62.3)	44 (55.0)	7.3 (-8.0, 22.7)
Muscle spasms	38 (49.4)	27 (33.8)	15.6 (0.4, 30.8)
Pain in extremity	7 (9.1)	2 (2.5)	6.6 (-0.7, 13.9)
Hepatobiliary disorders	4 (5.2)	0 (0.0)	5.2 (0.2, 10.2)
General disorders and administration site conditions	32 (41.6)	30 (37.5)	4.1 (-11.2, 19.3)
Malaise	4 (5.2)	0 (0.0)	5.2 (0.2, 10.2)
Infections and infestations	46 (59.7)	45 (56.2)	3.5 (-11.9, 18.9)
Upper respiratory tract infection	12 (15.6)	8 (10.0)	5.6 (-4.8, 16.0)
Blood and lymphatic system disorders	5 (6.5)	3 (3.8)	2.7 (-4.2, 9.6)
Anemia	4 (5.2)	0 (0.0)	5.2 (0.2, 10.2)
Metabolism and nutrition disorders	25 (32.5)	25 (31.2)	1.2 (-13.4, 15.8)
Hyperkalemia	11 (14.3)	5 (6.2)	8.0 (-1.4, 17.5)
Dehydration	4 (5.2)	0 (0.0)	5.2 (0.2, 10.2)

Source: Reviewer's analysis
[a] Absolute Risk Difference > 5%
[b] Difference is shown between Bardoxolone and Placebo
Abbreviations: CI, confidence interval; TEAE, treatment-emergent adverse event.

Table 26. FDA MedDRA Queries Occurring at 5% Higher Frequency in Treatment Arm Than Comparator Arm,[a] Phase 3 Safety Population, CARDINAL Phase 3

TEAE[b]	Bardoxolone N=77 n (%)	Placebo N=80 n (%)	Absolute Risk Difference (95% CI)[d]
System Organ Class *FDA Medical Query (Broad)*[c] Preferred Term			
Hepatobiliary disorders			
Hepatic injury	41 (53.2)	2 (2.5)	50.7 (39.1, 62.4)
Alanine aminotransferase increased	36 (46.8)	2 (2.5)	44.3 (32.6, 55.9)
Aspartate aminotransferase increased	19 (24.7)	1 (1.2)	23.4 (13.5, 33.4)
Hepatic failure	4 (5.2)	0 (0.0)	5.2 (0.2, 10.2)

TEAE[b]	Bardoxolone N=77 n (%)	Placebo N=80 n (%)	Absolute Risk Difference (95% CI)[d]
System Organ Class *FDA Medical Query (Broad)*[c] Preferred Term			
Musculoskeletal and connective tissue disorders			
Myalgia	39 (50.6)	30 (37.5)	13.1 (-2.3, 28.6)
Muscle spasms	38 (49.4)	27 (33.8)	15.6 (0.4, 30.8)
Gastrointestinal disorders			
Diarrhea	16 (20.8)	12 (15.0)	5.8 (-6.2, 17.8)
Diarrhea	12 (15.6)	6 (7.5)	8.1 (-1.9, 18.0)
Nausea	16 (20.8)	12 (15.0)	5.8 (-6.2, 17.8)
Vomiting	7 (9.1)	3 (3.8)	5.3 (-2.3, 13.0)
Dyspepsia	14 (18.2)	10 (12.5)	5.7 (-5.6, 16.9)
Vascular disorders			
Hemorrhage	13 (16.9)	6 (7.5)	9.4 (-0.8, 19.5)
Epistaxis	7 (9.1)	0 (0.0)	9.1 (2.7, 15.5)
Respiratory, thoracic and mediastinal disorders			
Cough	9 (11.7)	3 (3.8)	7.9 (-0.4, 16.2)
Cough	8 (10.4)	3 (3.8)	6.6 (-1.3, 14.6)
Nervous system disorders			
Dysgeusia	7 (9.1)	2 (2.5)	6.6 (-0.7, 13.9)
General disorders and administration site conditions			
Fatigue	19 (24.7)	15 (18.8)	5.9 (-7.0, 18.8)
Malaise	4 (5.2)	0 (0.0)	5.2 (0.2, 10.2)
Blood and lymphatic system disorders			
Anemia	5 (6.5)	1 (1.2)	5.2 (-0.8, 11.3)
Anemia	4 (5.2)	0 (0.0)	5.2 (0.2, 10.2)

Source: Reviewer's analysis
[a] Absolute Risk Difference >5%
[b] Treatment-Emergent AEs defined as occurring within 30 days
[c] Version 2020_01_29
[d] Difference is shown between Bardoxolone and Placebo
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

Table 27. Adverse Events of Special Interest, Renal, CARDINAL Phase 3

Adverse Event	Bardoxolone N=77 n (%)	Placebo N=80 n (%)	Absolute Risk Difference (95.0% CI)[a]
Grouping Related to AESI	18 (23.4)	15 (18.8)	4.6 (-8.1, 17.4)
Acute kidney injury	2 (2.6)	0 (0.0)	2.6 (-1.0, 6.2)
Glomerular filtration rate decreased	2 (2.6)	0 (0.0)	2.6 (-1.0, 6.2)
Proteinuria	8 (10.4)	7 (8.8)	1.6 (-7.6, 10.8)
Albuminuria	2 (2.6)	1 (1.2)	1.3 (-3.0, 5.7)
Urine output decreased	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Chronic kidney disease	2 (2.6)	2 (2.5)	0.1 (-4.8, 5.0)
End stage renal disease	2 (2.6)	2 (2.5)	0.1 (-4.8, 5.0)
Blood urea increased	1 (1.3)	1 (1.2)	0.0 (-3.5, 3.6)
Blood creatinine increased	3 (3.9)	8 (10.0)	-6.1 (-14.0, 1.8)
Serious	4 (5.2)	3 (3.8)	1.4 (-5.0, 7.9)
Fatal outcome	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Life-threatening	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)

Adverse Event	Bardoxolone N=77 n (%)	Placebo N=80 n (%)	Absolute Risk Difference (95.0% CI)[a]
Requiring hospitalization	1 (1.3)	2 (2.5)	-1.2 (-5.5, 3.1)
Persist or Signif Disability/Incapacity	1 (1.3)	0 (0.0)	1.3 (-1.2, 3.8)
Congenital anomaly or birth defect	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Other	2 (2.6)	1 (1.2)	1.3 (-3.0, 5.7)
Resulting in discontinuation	4 (5.2)	2 (2.5)	2.7 (-3.3, 8.7)
Maximum severity			
Mild	5 (6.5)	8 (10.0)	-3.5 (-12.1, 5.1)
Moderate	10 (13.0)	6 (7.5)	5.5 (-4.0, 15.0)
Severe	3 (3.9)	1 (1.2)	2.6 (-2.3, 7.6)

Source: Reviewer's analysis
[a] Difference is shown between bardoxolone and placebo
Abbreviations: AE, adverse event; AESI, adverse event of special interest.

Table 28. Treatment-Emergent Adverse Events[a] Occurring at 1% Higher Frequency in Treatment Arm Than Comparator Arm, Phase 3 Safety Population, BEACON

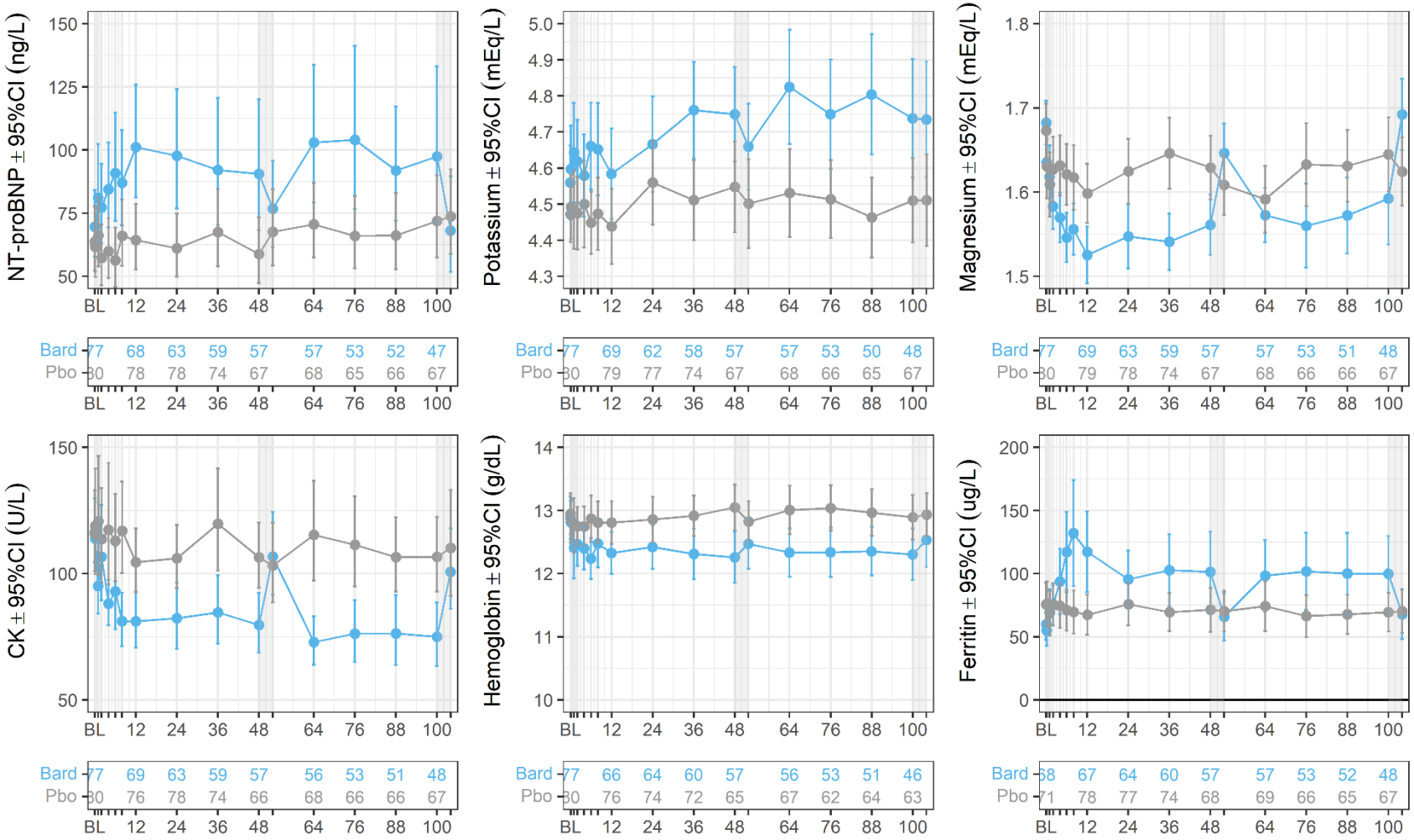
TEAE[b]	Bardoxolone N=1092 n (%)	Placebo N=1093 n (%)	Absolute Risk Difference (95.0% CI)[c]
Body System or Organ Class Preferred Term			
Musculoskeletal and connective tissue disorders	593 (54.3)	360 (32.9)	21.4 (17.3, 25.4)
Muscle spasms	460 (42.1)	169 (15.5)	26.7 (23.0, 30.3)
Musculoskeletal pain	28 (2.6)	15 (1.4)	1.2 (0.0, 2.4)
Myalgia	28 (2.6)	15 (1.4)	1.2 (0.0, 2.4)
Investigations	384 (35.2)	186 (17.0)	18.1 (14.5, 21.8)
Weight decreased	222 (20.3)	43 (3.9)	16.4 (13.7, 19.0)
Gamma-glutamyltransferase increased	47 (4.3)	9 (0.8)	3.5 (2.2, 4.8)
Metabolism and nutrition disorders	582 (53.3)	447 (40.9)	12.4 (8.2, 16.6)
Hypomagnesemia	234 (21.4)	61 (5.6)	15.8 (13.1, 18.6)
Decreased appetite	210 (19.2)	87 (8.0)	11.3 (8.4, 14.1)
Nervous system disorders	330 (30.2)	231 (21.1)	9.1 (5.4, 12.7)
Dysgeusia	85 (7.8)	9 (0.8)	7.0 (5.3, 8.6)
Ageusia	39 (3.6)	0 (0.0)	3.6 (2.5, 4.7)
Respiratory, thoracic and mediastinal disorders	305 (27.9)	215 (19.7)	8.3 (4.7, 11.8)
Epistaxis	46 (4.2)	18 (1.6)	2.6 (1.2, 4.0)
Cough	69 (6.3)	44 (4.0)	2.3 (0.4, 4.1)
Dyspnea	112 (10.3)	95 (8.7)	1.6 (-0.9, 4.0)
Cardiac disorders	233 (21.3)	154 (14.1)	7.2 (4.1, 10.4)
Cardiac failure congestive	81 (7.4)	50 (4.6)	2.8 (0.9, 4.8)
Atrial fibrillation	35 (3.2)	12 (1.1)	2.1 (0.9, 3.3)
Cardiac failure	14 (1.3)	3 (0.3)	1.0 (0.3, 1.7)
Gastrointestinal disorders	465 (42.6)	394 (36.0)	6.5 (2.4, 10.6)
Nausea	211 (19.3)	160 (14.6)	4.7 (1.5, 7.8)
Vomiting	126 (11.5)	91 (8.3)	3.2 (0.7, 5.7)
Abdominal pain	44 (4.0)	23 (2.1)	1.9 (0.5, 3.4)
Gastroesophageal reflux disease	25 (2.3)	13 (1.2)	1.1 (0.0, 2.2)
General disorders and administration site conditions	402 (36.8)	342 (31.3)	5.5 (1.6, 9.5)
Fatigue	170 (15.6)	127 (11.6)	3.9 (1.1, 6.8)
Edema peripheral	201 (18.4)	179 (16.4)	2.0 (-1.1, 5.2)

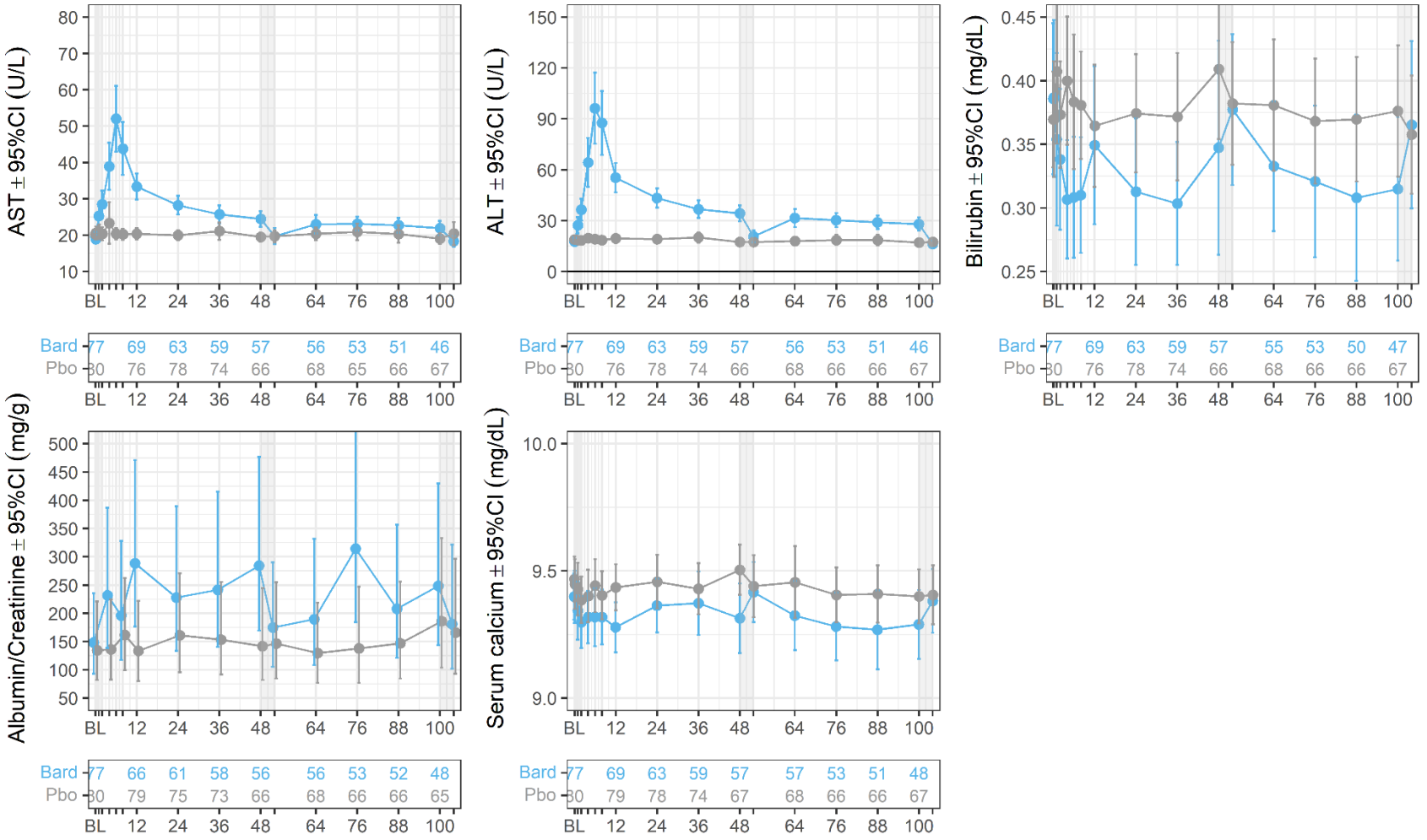
TEAE[b]	Bardoxolone N=1092 n (%)	Placebo N=1093 n (%)	Absolute Risk Difference (95.0% CI)[c]
Body System or Organ Class Preferred Term			
Blood and lymphatic system disorders	114 (10.4)	69 (6.3)	4.1 (1.8, 6.4)
Anemia	89 (8.2)	46 (4.2)	3.9 (1.9, 6.0)
Infections and infestations	391 (35.8)	349 (31.9)	3.9 (-0.1, 7.8)
Pneumonia	51 (4.7)	25 (2.3)	2.4 (0.8, 3.9)
Hepatobiliary disorders	31 (2.8)	16 (1.5)	1.4 (0.2, 2.6)
Psychiatric disorders	141 (12.9)	127 (11.6)	1.3 (-1.5, 4.0)
Vascular disorders	189 (17.3)	184 (16.8)	0.5 (-2.7, 3.6)
Hypertension	119 (10.9)	98 (9.0)	1.9 (-0.6, 4.4)

Source: Reviewer's analysis
[a] Absolute risk difference >1%
[b] Treatment-emergent AEs defined as occurring within 30 days
[c] Difference is shown between bardoxolone and placebo
Abbreviations: CI, confidence interval.

6.7.5. Laboratory Parameters

Figure 21. Laboratory Parameters, CARDINAL Phase 3

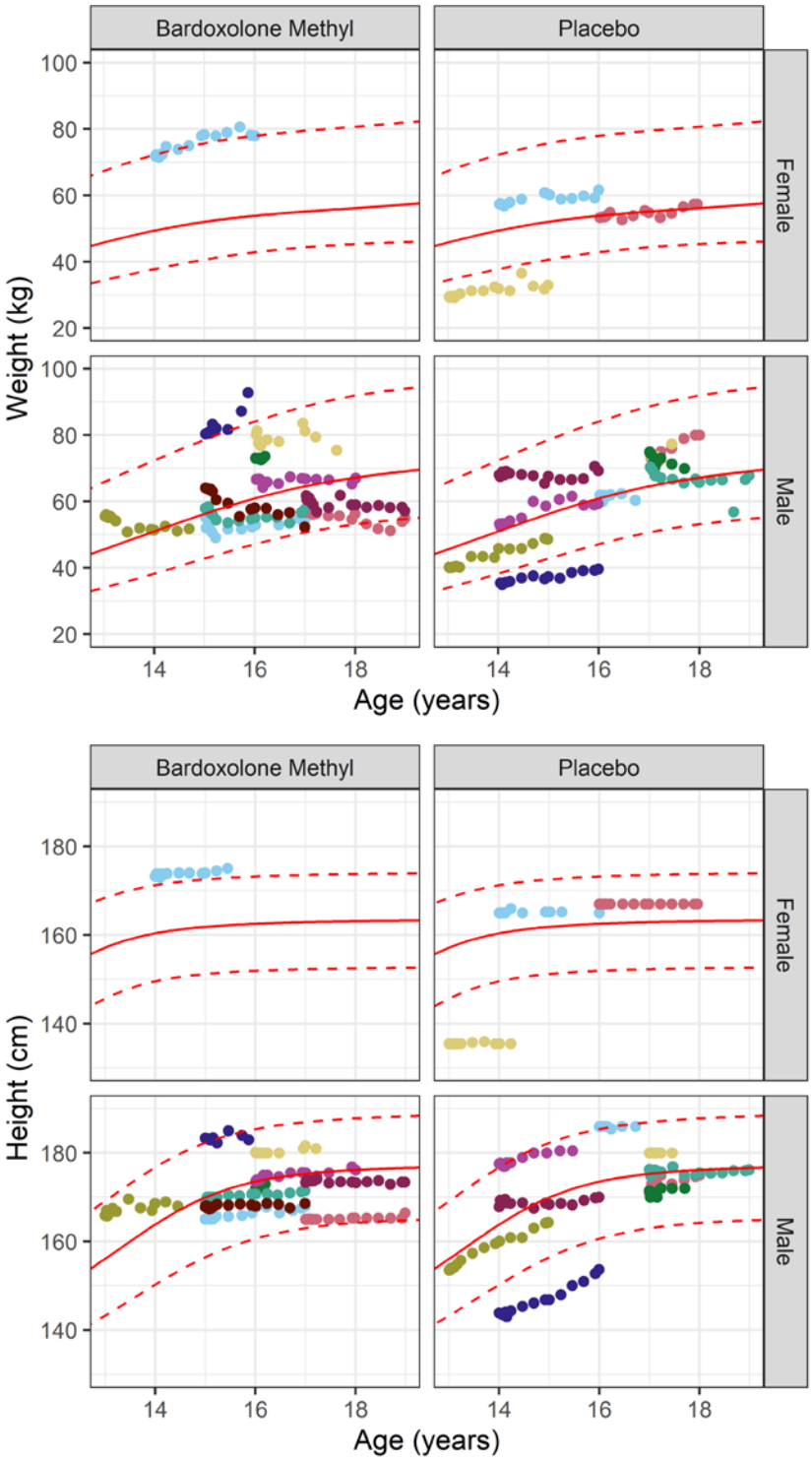




Source: Reviewer's analysis
Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; Bard, bardoxolone; BL, baseline; BNP, B-type natriuretic peptide; CK, creatinine kinase; Pbo, placebo.

6.7.6. Growth Charts

Figure 22. Growth Charts, CARDINAL Phase 3



Source: Reviewer's analysis

The colored dots correspond to individual patient data. The same color is used for weight and height for the same combination of treatment and sex. The solid red and dashed red lines represent CDC's clinical growth data for the median (solid) and 5th and 95th percentile (dashed).

6.8. Drug-Induced Liver Injury

Division of Hepatology and Nutrition Consultation

Drug-induced Liver Injury Team

NDA	215484
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	bardoxolone methyl (RTA-402)
Indication	Alport Syndrome
Applicant	Reata Pharmaceuticals, Inc.
Requesting Division	Division of Cardiology and Nephrology (DCN)
Primary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Reviewer **Office of Pharmacoepidemiology**	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Joseph Toerner, MD, MPH Director, OND/DHN
Assessment Date	Sep 19, 2021

Context: Bardoxolone (BDX) is an oral, small molecule that activates nuclear factor erythroid 2-related factor (Nrf2) by binding the Kelch-like ECH-associated protein 1 (Keap1). Nrf2 is a transcription factor important in the activation of antioxidant pathways thus attenuating inflammation and oxidative stress. The sponsor submits BDX as an NDA for the treatment of Alport Syndrome (AS) a rare genetic disorder which causes progressive renal failure in children and young adults. BDX was also studied in a phase 2b and phase 3 trial for chronic kidney disease (CKD) associated with type 2 diabetes. Unfortunately, BDX was associated with increased heart failure in the phase 3 study, and the sponsor has turned its attention to more uncommon CKD diseases. In the pivotal trials for AS and trials for diabetes associated CKD elevations in transaminases with BDX exposure were more common compared to placebo. The Division of Cardiology and Nephrology (DCN) requested the DILI Team provide "guidance" on their "approach to evaluate the potential risk of liver toxicity" and to provided "assistance with the development of a risk mitigation strategy" if needed.

Executive Summary: We do not see a liver injury issue that would jeopardize approval for this agent. The sponsor's suggestion that liver enzyme elevations are a benign off-target effect of BDX is plausible. In vitro studies suggest BDX increases transaminase mRNA production. This increased mRNA would be in line with Nrf-2 function as promoter of gene expression. The sponsor included liver safety data from their larger diabetic CKD trials, so the number of subjects exposed to BDX is over 1000. Enzyme elevations were modest without bilirubin increase. There were no Hy's Law cases. Elevations typically declined with continued BDX exposure and resolved rapidly with stopping BDX suggesting enzyme induction without significant injury. Nevertheless, liver enzyme elevations were common, and labeling should address this finding should BDX be approved. Full assessment and recommendations are in Section 5.0.

Consultation Sections:

Section 1.0 - Rationale
Section 2.0 - ADME data pertinent to DILI
Section 3.0 - Non-clinical data pertinent DILI
Section 4.0 - Clinical data: eDISH, summary tables and DILI case level assessments
Section 5.0 – Assessment & Recommendations

Abbreviations:
ALP: alkaline phosphatase
ALT: alanine aminotransferase
AS: Alport Syndrome
AST: aspartate aminotransferase
BDX: bardoxolone methyl
CKD: chronic kidney disease
DILI: drug-induced liver injury
DMC: Data Monitoring Committee
ESRD: end-stage renal disease
IP: investigational product
KEAP1: Kelch-like ECH-associated protein 1
MOA: mechanism of action
MOD: mechanism of DILI
Nrf2: nuclear factor erythroid 2-related factor
ULN: upper limit of normal

1.0 Rationale for use

1.1 Alport Syndrome: Alport syndrome (AS) is a rare, serious, and progressive genetic disease with significant unmet medical needs.[1] Its global prevalence is unknown but estimated to affect 30,000 to 60,000 people in the US. Three genetic forms exist: X-linked, autosomal recessive and autosomal dominant. The X-linked form is most common. Clinical manifestations include progressive renal failure, hearing loss, and eye abnormalities There is no approved treatment. Nephropathy is associated with an increased risk for progression to end stage renal disease (ESRD). Renal failure occurs between age 16 and 35 years in the X-linked and autosomal recessive forms.[2] Thus, it has significant negative impacts on quality of life and life expectancy. The sponsor is seeking Priority Review and Rare Pediatric Priority Review Voucher.

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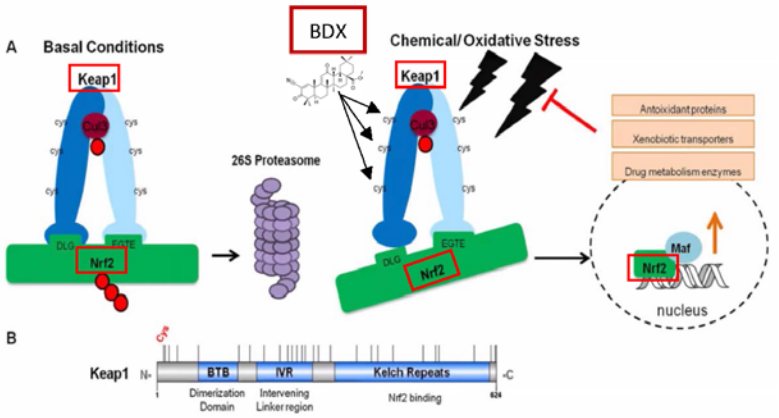
[1] https://rarediseases.info.nih.gov/diseases/5785/alport-syndrome (accessed Jun 1, 2021)
[2] UpToDate https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-treatment-of-alport-syndrome-hereditary-nephritis?search=alport%20syndrome&source=search_result&selectedTitle=1~43&usage_type=default&display_rank=1 (accessed Jun 1, 2021)

Pathophysiology centers on defects in 3 collagen related genes, COL 4A3, 4A4 and 4A5. Each provides instructions on making type IV collagen, which is critical to the structure and function of glomeruli, organ of Corti (inner ear) and the eye (lens and retinal cells). The abnormal structure of type IV collagen defects is felt to lead to chronic inflammation and long-term damage.

1.2 Mechanism of Drug Action: Bardoxolone (BDX) is new molecular entity related to oleanolic acid-derived synthetic triterpenoid compounds. It activates the Keap1-Nrf2 pathway by interacting with Keap1, a Nrf2 repressor. Nrf2 is then freed to translocate to the nucleus where it activates promoter regions of antioxidant genes (Figure 1). Therefore, BDX is hypothesized to decrease inflammation post-injury or other insults that arise with type IV collagen dysregulation.

Figure 1 BDX postulated MOA:

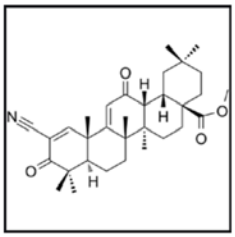


Typically, oxidative stress interacts with cysteine residues of Keap1 which causes release of Nrf2 as negative feedback. The sponsor postulates that BDX will bind Keap1 to cause similar feedback in AS patients.

2.0 Pharmacokinetic data relevant to DILI:

2.1 Chemical structure (Figure 2):

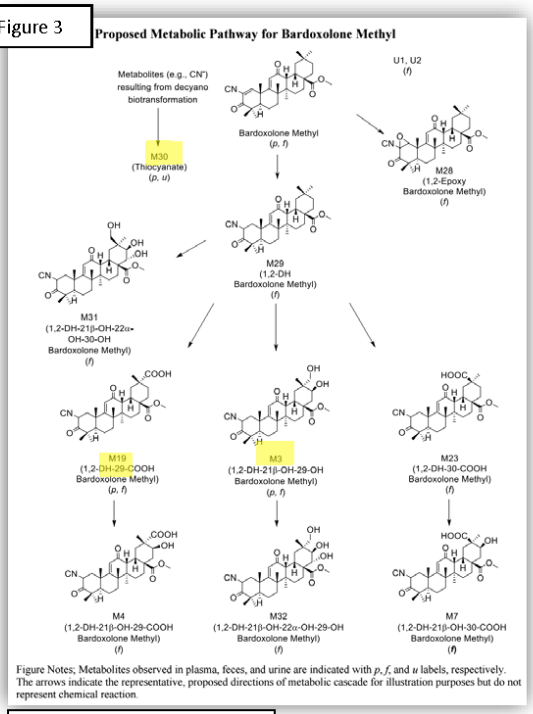
Figure 2



2.2 Absorption of oral dosing is relatively quick with median t-max of 2 to 5 hours in healthy volunteers. Volume of distribution is large with higher distribution predicted for those with hepatic impairment (see 2.4).

2.3 Metabolism and Elimination: BDX is metabolized via several CYP450 enzymes but CYP3A4 and CYP3A5 are dominant. Three pharmacologically inactive metabolites are formed (M3, M30 and M19) making up 91% of C-14 radioactivity in human plasma (Figure 3). Of the three, M30 is a thiocyanate and predominate at 76%. However, study drug related thiocyanate levels were similar to endogenous levels in healthy controls. Elimination is predominantly via feces at 81% by carbon-14 studies and only 6% in urine which includes the thiocyanate metabolite.

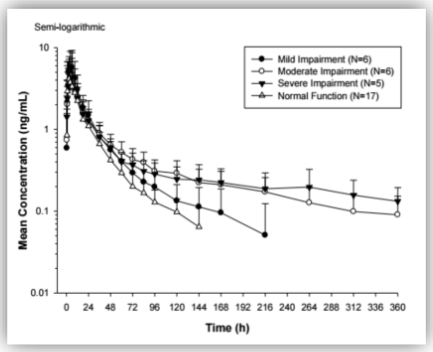
Figure 3



Seq 1, 4.2.2.4, RTA-P-15072, p. 29

2.4 Hepatic impairment (HI) studies suggest up to 84% higher BDX exposure by AUC in moderate to severe HI patients compared to healthy adults on single dose studies (Figure 4).

Figure 4



3.0 Non-clinical Data on Liver Injury

3.1 Animal studies: Some animal studies showed liver injury on histology, particularly at higher doses, while others did not. In CByB6F1-Tg(HRAS)2Jic Wild Type (rasH2) mice, doses > 15 mg/kg/day induced hepatic necrosis with elevated ALT and AST in the 28-day dosing studies, but this was in the setting of "multi-organ toxicity" with bone marrow and gastric involvement. Below 15 mg/kg/day liver changes were limited to hypertrophy and increase in liver weight. The NOAEL was determined to be 5mg/kg/d in this study.

In 28-day Sprague-Dawley rat studies, BDX was poorly tolerated overall with mortalities of no "specific cause". Rats were found to have decreased activity, audible breathing, hunched posture and distended abdomens. Decreased feeding was see at all doses. Liver hypertrophy and bile duct hyperplasia was seen. In females, increased transaminases and GGT were seen. Other organs with histopathology included kidneys, stomach, bladder, and thymus. NOAEL could not be determined because findings were seen at all dose levels.

Similarly, 6-month Sprague-Dawley rat studies had mortalities with histopathology across several organs. At this longer exposure, macroscopic examination showed cysts in the liver. Microscopic examination confirmed "cholangiomas, bile duct hyperplasia, biliary cysts and hepatocellular hyperplasia". As with the rat studies, NOAEL could not be determined. Male Syrian Golden hamster were also intolerant up to 34 days of exposure. Nine-month beagle dog studies had significant gastrointestinal toxicity of unclear mechanism at all doses. The study was stopped at 26 weeks, and NOAEL could not be determined. There was no mention of liver injury in the dogs.

On the other hand, cynomolgus monkeys exposed for 28 days and 12 months tolerated BDX well. The monkeys had only increased liver weights with minimal to mild bile duct changes, and no liver enzyme changes compared to

controls. NOAELs were 150 mg/kg/d (28-days exposure) and 300 mg/kg/d (12-month exposure). Gottingen minipigs also tolerated BDX well with livers showing minimal mononuclear cell infiltration only. NOAEL was 30 mg/kg/d.

3.2 Bile acid secretion: The sponsor studied BDX's effects on bile acid secretion using Matrigel/Collagen sandwich culture system. Carboxydichlofofluorescein (CDF) was used to monitor bile acid secretion. BDX did inhibit bile acid secretion in rat, but not human or monkey hepatocytes. Likewise, BDX suppressed BSEP mRNA expression in rat but not human hepatocytes. Instead, BDX induced BSEP mRNA expression. These differences might explain the liver changes seen in rats, but not monkeys (see Section 3.1). This reviewer found no glutathione trapping, or mitochondrial toxicity studies.

3.3 Transporter studies: In vitro vesicle studies suggest BDX is a weak substrate for OATP1B1, but not OATP1B3. It is not a substrate for P-gp or BCRP. M3 and M19 inhibit OATP1B1 and OATP1B3. Neither inhibits P-gp, BCRP, OAT1, OAT3, OCT2, MATE1, or MATE2-K. There was no significant inhibition of BSEP at the highest dosing tested, so an IC50 could not be determined.

3.4 BDX effects on ALT and AST expression: Based on animal and in vitro studies, the sponsor suggests that BDX induces ALT and AST expression without liver damage (Figure 5).[3]

3.4.1 The sponsor used knockout and knockdown mouse models to look at ALT, AST, and mRNA levels. Nrf2-null and Keap1-knockdown mice had lower and higher ALT levels, respectively compared to wild-type. These changes corresponded to lower and higher mRNA ALT1 and ALT2 levels (Figure 5). The authors analyzed both liver and kidney tissue. ALT isoenzymes are not used in clinical practice. Both are found in liver and have the same function.[4] There are animal data to suggest isozymes 1 is more specific to liver injury.[5]

Figure 5

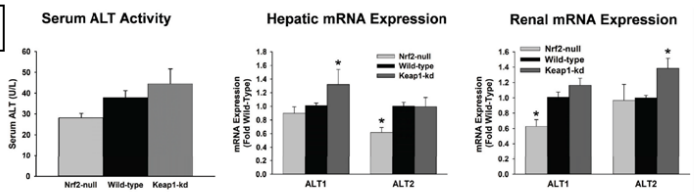


Figure S4. Serum ALT Activity and ALT mRNA Expression in Wild-type, Nrf2-Null, and Keap1-Knockdown Mice
Serum was collected from 8-week-old wild-type [n=8], Nrf2-null [n=8], and Keap1-kd [n=9] mice. ALT activity was determined utilizing a commercially available clinical chemistry analyzer. Hepatic mRNA expression of ALT1 and ALT2 were quantified by qRT-PCR in C57Bl/6 wild type [n=7], Nrf2-null [n=7], and Keap1-kd [n=9] mice. Renal mRNA expression of ALT1 and ALT2 were quantified by qRT-PCR in 8-week-old C57Bl/6 wild-type [n=4], Nrf2-null [n=3], and Keap1-kd [n=4] mice. *indicates a statistically significant difference from wild-type mice [p<0.05].

3.4.2 Several cell lines were analyzed for ALT and AST expression by analysis of cDNA without and with increasing BDX exposure. While

[3] Lewis JH, et al. Clin Transl Sci (2021)
[4] Yang RZ, et al. Hepatology (2009)
[5] Rafter I, et al. Int J Mol Med (2012)

there was some variation between cell lines, mRNA for ALT1 and AST1 typically increased with increasing exposure (Figure 6). The sponsor confirmed increase expression of NQO1, a Nrf2 target gene, indicating on target effects of BDX in these cDNA experiments.

Figure 6

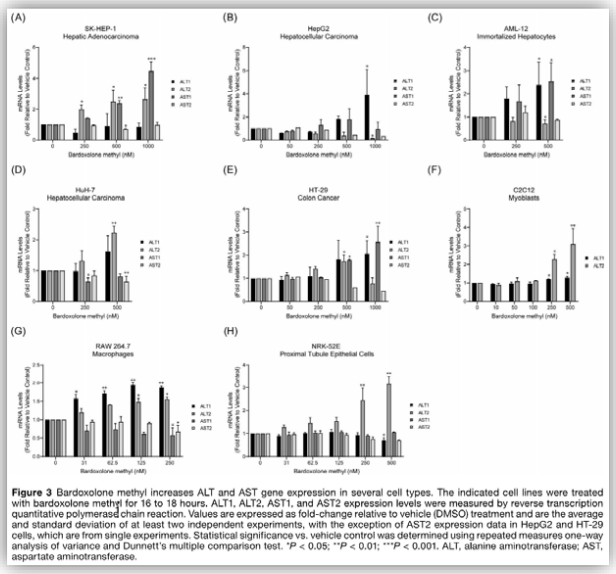


Figure 3 Bardoxolone methyl increases ALT and AST gene expression in several cell types. The indicated cell lines were treated with bardoxolone methyl for 16 to 18 hours. ALT1, ALT2, AST1, and AST2 expression levels were measured by reverse transcription quantitative polymerase chain reaction. Values are expressed as fold-change relative to vehicle (DMSO) treatment and are the average and standard deviation of at least two independent experiments, with the exception of AST2 expression data in HepG2 and HT-29 cells, which are from single experiments. Statistical significance vs. vehicle control was determined using repeated measures one-way analysis of variance and Dunnett's multiple comparison test. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

4.0 Clinical Data on DILI

4.1 BEAM Study[6]: This study was a Phase 2, double blind, randomized clinical trial of BDX at 3 different doses versus placebo in 227 adults with chronic kidney disease (CKD). Treatment was for 52 weeks including a upward dose tapering up at the start. Elevated ALT in the BDX was frequent at 71%. Elevations were "mild" and peaked at 2-4 weeks of treatment start or dose increase. Only 18 (11%) of patients had elevations over 3x ULN. No persistent elevations were seen despite continuing BDX. There were no cases of jaundice or other signs of liver failure.

4.2 BEACON Study[7]: This study was a Phase 3, double blind, randomized clinical trial of BDX (20 mg orally per day) versus placebo in 2185 adults with type 2 diabetes and stage 4 CKD. The trial was terminated early due to increased heart failure hospitalizations and cardiovascular events (including death) in the BDX group. Median follow-up was 9 months. Median investigational drug

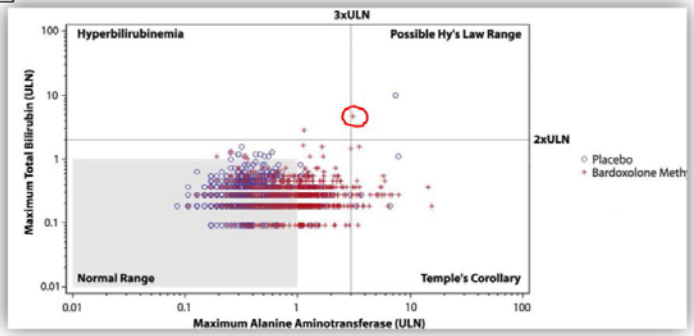
[6] Pergola PE, et al. N Engl J Med (2011)

[7] de Zeeuw D, et al. N Engl J Med (2013)

exposure was 7-8 months. No liver enzyme data appear in the primary publication but are reviewed in detail in a subsequent paper.[8]

eDISH plot in this later paper shows only one BDX case in the right upper quadrant (bilirubin approximately 4.5 xULN [or bilirubin 5.4 mg/dL] and ALT 3 x ULN), and the investigators assessed this case as non-DILI in favor of a choledocholithiasis (Figure 7). No further details are provided. There was an imbalance in Temple's Corollary.

Figure 7



Shift tables also show ALT elevations were more frequent in the BDX arms with two cases having ALT ≥ 8 xULN. However, the majority of elevations in ALT were in the >ULN to <3x ULN range. Nearly all patients had normal transaminases at baseline. (Table 1)

Table 1 Shift in ALT (U/L) from baseline to maximum post-baseline value while on study drug in BEACON

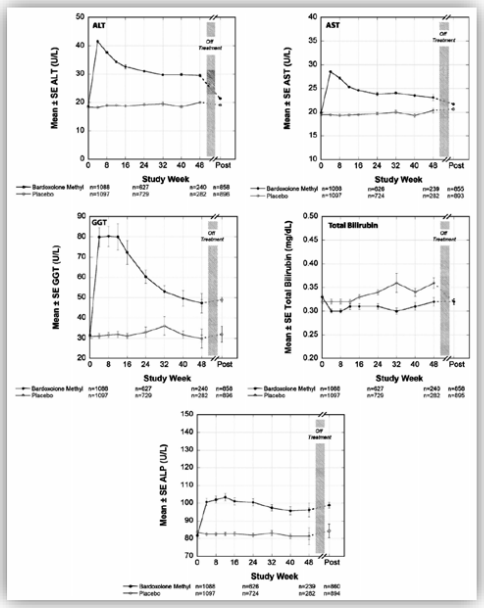
Treatment group/baseline ALT	Maximum post-baseline value while on treatment					
	≤ULN	>ULN to < 3 × ULN	≥3 × ULN to < 5 × ULN	≥5 × ULN to < 8 × ULN	≥8 × ULN	No post-baseline value
Placebo [n = 1097]						
ALT ≤ ULN [n = 1096; %]	1,023 [93]	50 [5]	2 [<1]	1 [<1]	0	20 [2]
>ULN to < 3 × ULN [n = 1]	0	1 [<1]	0	0	0	0
≥3 × ULN to < 5 × ULN [n = 0]	0	0	0	0	0	0
≥5 × ULN to < 8 × ULN [n = 0]	0	0	0	0	0	0
≥8 × ULN [n = 0]	0	0	0	0	0	0
Bardoxolone Methyl [n = 1,088]						
ALT ≤ ULN [n = 1086; %]	610 [56]	380 [35]	18 [2]	9 [1]	2 [< 1]	67 [6]
>ULN to < 3 × ULN [n = 2]	0	0	1 [< 1]	1 [< 1]	0	0
≥3 × ULN to < 5 × ULN [n = 0]	0	0	0	0	0	0
≥5 × ULN to < 8 × ULN [n = 0]	0	0	0	0	0	0
≥8 × ULN [n = 0]	0	0	0	0	0	0

Mean liver enzyme and bilirubin changes occurred early and declined to plateau over time. All means were higher in the BDX group except bilirubin which was lower. ALT and AST declined back to baseline off BDX, though

[8] Lewis JH, et al. Clin Transl Sci (2020)

time of decline were not provided. Mean increases were < 2-3 x ULN for ALT, AST and alkaline phosphatase (ALP) (Figure 8).

Figure 8

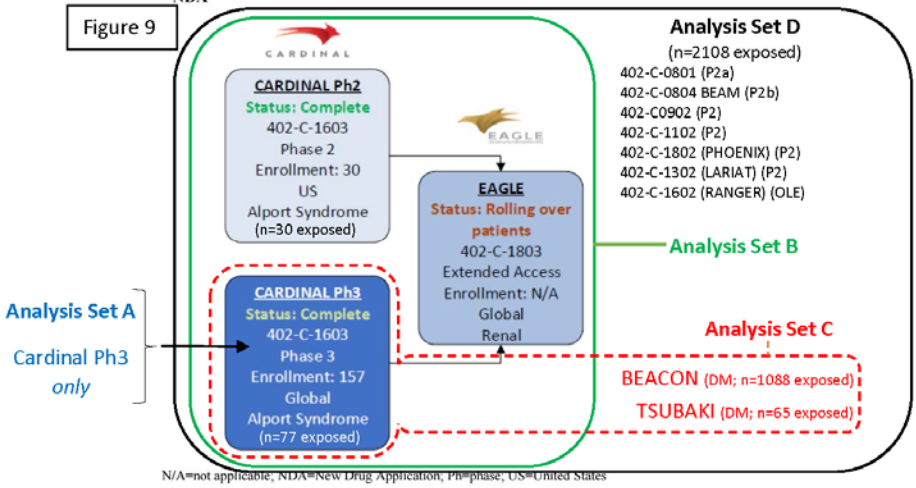


4.3 Clinical trials for this NDA.

4.3.1 The NDA and Integrated Summary of Safety is based on 3 studies, Cardinal phase 2, Cardinal phase 3 and Eagle roll over study (Analysis Set B). However, three other analysis sets exist with Set D being the most encompassing (Figure 9).

Figure 9

Bardoxolone Methyl Clinical Trials Contributing to the Alport Syndrome NDA



N/A=not applicable; NDA=New Drug Application; Ph=phase; US=United States

4.4 Summary changes in liver tests in the ISS

4.4.1 Mean transaminase changes over time for Analysis Set A (Cardinal Phase 3) were similar to what was seen with the BEACON trial. BDX dosing was 20 to 30 mg maximum and based on urinary albumin to creatine ratio. The protocol had a 4-week gap in therapy for all patients (Figure 10a and 10b).

Figure 10a **Mean ALT Over Time (Safety Population)**

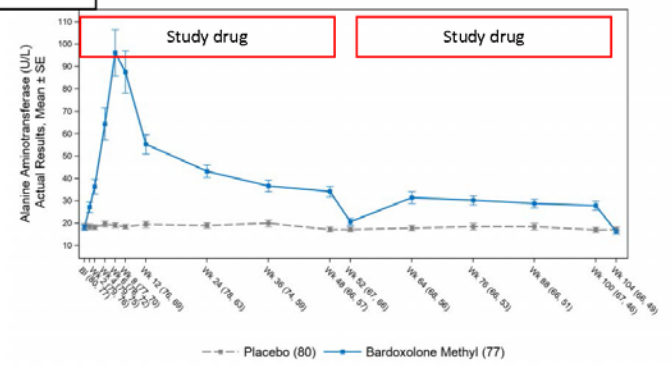
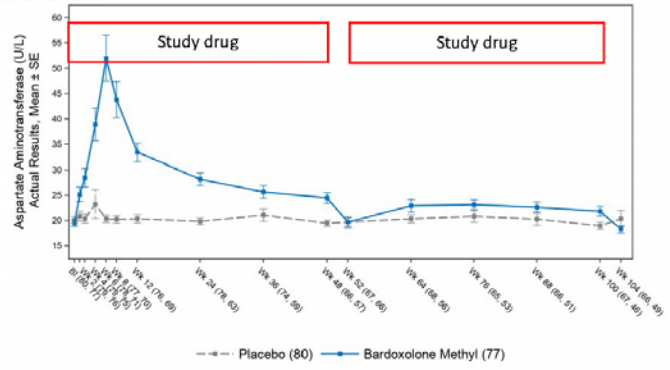
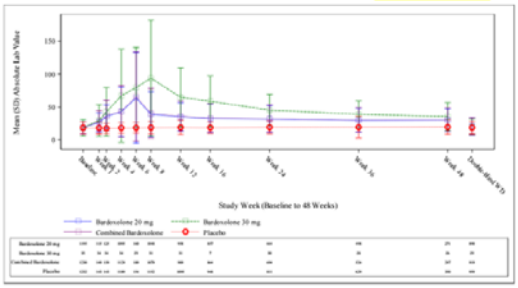


Figure 10b **Mean AST Over Time (Safety Population)**



4.4.2 Mean ALTs baseline to week 48 in Analysis C (Figure 11)

Figure 11



Abbreviations: ALT=alanine aminotransferase; CKD=chronic kidney disease; Lab=laboratory; SD=standard deviation, WD=withdrawal

4.4.3 Elevations in liver tests compared to placebo in the overall ISS: The proportions of elevated liver enzymes were higher with BDX (RTA-402) (Table 2), reflecting the increased mean ALT and AST shown in Section 4.4.2. There were more patients with elevation in liver enzymes in the cohorts with higher dosing of BDX. There were three cases on BDX with bilirubin >2x ULN and these are discussed in Section 4.5 (Case level analysis).

Table 2

Frequency of Hepatic Safety Laboratory Parameter Elevations at any Post-Baseline Visit

Lab Name	RTA-402 150 MG (N = 76)	RTA-402 75 MG (N = 77)	RTA-402 30 MG (N = 14)	RTA-402 25 MG_75 MG (N = 20)	RTA-402 25 MG (N = 77)	RTA-402 15 MG (N = 50)	RTA-402 10 MG (N = 28)	RTA-402 5 MG (N = 25)	RTA-402 2.5 MG (N = 14)	BARDOXOLONE METHYL (N = 1653)	PLACEBO (N = 1340)
ALT Elevations											
Less than 3x ULN	66 (86.8%)	69 (89.6%)	11 (78.6%)	19 (95%)	69 (89.6%)	50 (100%)	26 (92.9%)	25 (100%)	14 (100%)	1344 (81.3%)	1323 (98.7%)
Between 3x and 5x ULN	5 (6.6%)	6 (7.8%)	1 (7.1%)	1 (5%)	3 (3.9%)	0 (0%)	1 (3.6%)	0 (0%)	0 (0%)	79 (4.8%)	3 (0.2%)
Between 5x and 10x ULN	4 (5.3%)	0 (0%)	2 (14.3%)	0 (0%)	3 (3.9%)	0 (0%)	1 (3.6%)	0 (0%)	0 (0%)	55 (3.3%)	4 (0.3%)
Between 10x and 20x ULN	0 (0%)	2 (2.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (0.3%)	0 (0%)
AST Elevations											
Less than 3x ULN	70 (92.1%)	75 (97.4%)	12 (85.7%)	20 (100%)	73 (94.8%)	50 (100%)	27 (96.4%)	25 (100%)	14 (100%)	1423 (86.1%)	1325 (98.9%)
Between 3x and 5x ULN	4 (5.3%)	0 (0%)	1 (7.1%)	0 (0%)	1 (1.3%)	0 (0%)	1 (3.6%)	0 (0%)	0 (0%)	50 (3%)	3 (0.2%)
Between 5x and 10x ULN	1 (1.3%)	2 (2.6%)	1 (7.1%)	0 (0%)	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (0.4%)	1 (0.1%)
Between 10x and 20x ULN	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0.2%)	1 (0.1%)
ALP Elevations											
Less than 2x ULN	68 (89.5%)	73 (94.8%)	12 (85.7%)	20 (100%)	73 (94.8%)	49 (98%)	27 (96.4%)	25 (100%)	14 (100%)	1438 (87%)	1324 (98.8%)
Between 2x and 3x ULN	5 (6.6%)	3 (3.9%)	1 (7.1%)	0 (0%)	1 (1.3%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	22 (1.3%)	3 (0.2%)
3x ULN or Greater	2 (2.6%)	1 (1.3%)	1 (7.1%)	0 (0%)	1 (1.3%)	0 (0%)	1 (3.6%)	0 (0%)	0 (0%)	23 (1.4%)	3 (0.2%)
BILI Elevations											
Less than 2x ULN	75 (98.7%)	77 (100%)	14 (100%)	20 (100%)	74 (96.1%)	50 (100%)	28 (100%)	25 (100%)	14 (100%)	1481 (89.6%)	1329 (99.2%)
Between 2x and 5x ULN	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.1%)	0 (0%)
8x ULN or Greater	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
GGT Elevations											
Less than 2x ULN	18 (23.7%)	15 (19.5%)	4 (28.6%)	9 (45%)	28 (36.4%)	23 (46%)	13 (46.4%)	21 (84%)	11 (78.6%)	589 (35.6%)	1221 (91.1%)
2x ULN or Greater	43 (56.6%)	45 (58.4%)	10 (71.4%)	11 (55%)	36 (46.8%)	27 (54%)	15 (53.6%)	4 (16%)	3 (21.4%)	913 (55.2%)	119 (8.9%)

Discontinuations due to liver related AEs was also higher in the Cardinal study (Table 3). All were due to liver enzyme elevations.

AEs leading to discontinuation in CARDINAL

- There were more patients who discontinued due to AEs in the bardoxolone group (17 [22%] vs 4 [5%])
- Most common AEs associated with D/C:
  - LFT increase
  - BNP or NT-proBNP (PT) increase
  - Muscle spasms or
  - GERD

Table 3

CARDINAL, AEs leading to discontinuation, safety population

System Organ Class *FDA Medical Query (Broad)[3]* Preferred Term	Bardoxolone Methyl N=77 n (%)	Placebo N=80 n (%)	Absolute Risk Difference (95% CI)[4]
Patients with at least 1 AE leading to discontinuation	17 (22.1%)	4 (5.0%)	17.1 (8.7, 27.5)
Hepatobiliary disorders			
Hepatic injury	6 (7.8%)	0 (0.0%)	7.8 (1.8, 13.8)
Alanine aminotransferase increased	6 (7.8%)	0 (0.0%)	7.8 (1.8, 13.8)
Aspartate aminotransferase increased	3 (3.9%)	0 (0.0%)	3.9 (-0.4, 8.2)
Gamma-glutamyltransferase increased	1 (1.3%)	0 (0.0%)	1.3 (-1.2, 3.8)
Renal and urinary disorders			
Acute kidney injury	3 (3.9%)	0 (0.0%)	3.9 (-0.4, 8.2)
Acute kidney injury	1 (1.3%)	0 (0.0%)	1.3 (-1.2, 3.8)
Blood creatinine increased	1 (1.3%)	0 (0.0%)	1.3 (-1.2, 3.8)
Glomerular filtration rate decreased	1 (1.3%)	0 (0.0%)	1.3 (-1.2, 3.8)
Gastrointestinal disorders			
Dyspepsia	2 (2.6%)	0 (0.0%)	2.6 (-1.0, 6.2)
Gastrooesophageal reflux disease	2 (2.6%)	0 (0.0%)	2.6 (-1.0, 6.2)
Musculoskeletal and connective tissue disorders			
Myalgia	2 (2.6%)	0 (0.0%)	2.6 (-1.0, 6.2)
Muscle spasms	2 (2.6%)	0 (0.0%)	2.6 (-1.0, 6.2)
Skin and subcutaneous tissue disorders			
Alopecia	1 (1.3%)	0 (0.0%)	1.3 (-1.2, 3.8)
Alopecia	1 (1.3%)	0 (0.0%)	1.3 (-1.2, 3.8)
Unknown			
Hypotension	1 (1.3%)	0 (0.0%)	1.3 (-1.2, 3.8)
Dehydration	1 (1.3%)	0 (0.0%)	1.3 (-1.2, 3.8)
General disorders and administration site conditions			
Peripheral oedema	1 (1.3%)	1 (1.2%)	0.0 (-3.5, 3.6)
Oedema peripheral	1 (1.3%)	1 (1.2%)	0.0 (-3.5, 3.6)

Source: ard_ae1 **Software:** R

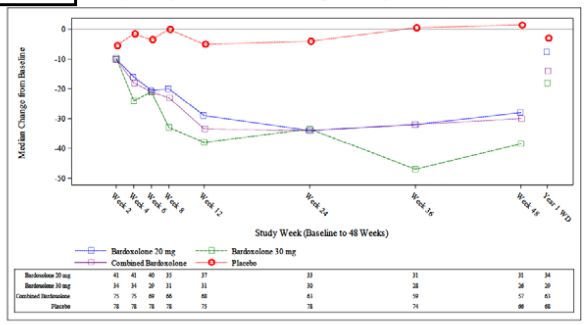
Abbreviations: N, number of patients in treatment arm; n, Number of patients with an event; CI, Confidence Interval; AE, Adverse Event

4.4.4 Search for other sources of transaminase elevation

4.4.4.1 Muscle injury is unlikely. Median CK levels fell in the treatment arms in Analysis Set A (Figure 12).

Figure 12

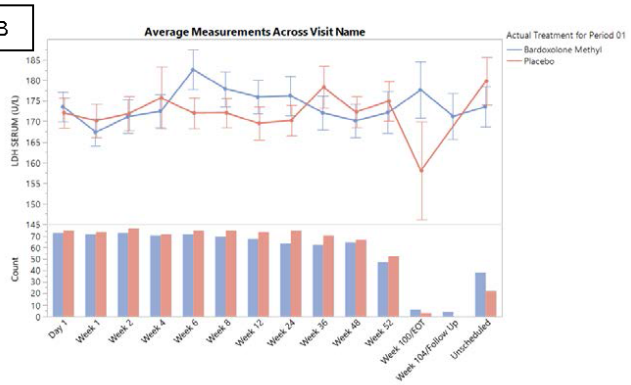
Median Change From Baseline in Creatine Kinase (U/L), Baseline to Week 48 (Primary Placebo-Controlled Alport Analysis Set A)



Bardoxolone 20 mg	41	41	40	35	37	33	31	31	34
Bardoxolone 10 mg	34	34	28	31	31	30	28	26	29
Combined Bardoxolone	75	75	68	66	68	63	59	57	63
Placebo	78	78	78	78	79	78	74	66	66

4.4.4.2 Hemolysis is unlikely. LDH levels were not significantly different between arms in Analysis Set B (Figure 13).

Figure 13



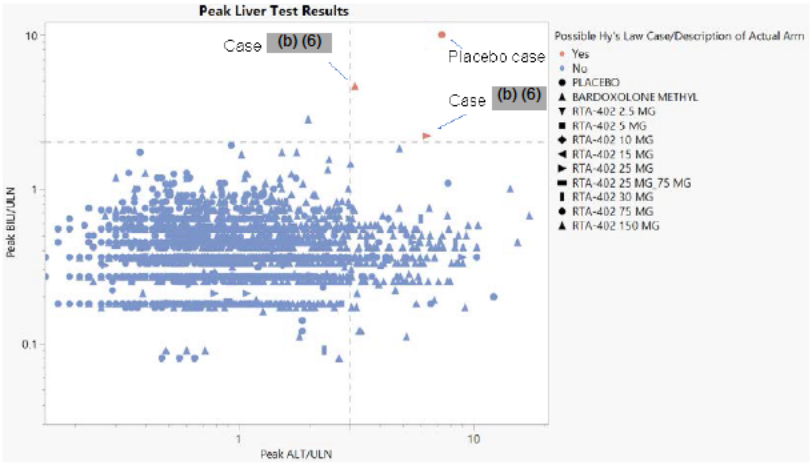
4.4.5 Chronic liver injury with persistent elevation in liver enzymes is difficult to assess without liver histology, but enzymes levels fell toward normal over time. Decline in platelet count that might indicate portal hypertension development was not seen in Analysis Set B (Figure 14).

Figure 14

4.4.6 Scatterplots (eDISH and cholestatic plot): Analysis Set D

4.4.6.1 eDISH: There were two cases in Analysis Set D that met transaminase and bilirubin criteria for Hy's Law, but both had features of cholestatic injury and could not be attributed to BDX with certainty (Figure 15). (AST was plot similar)

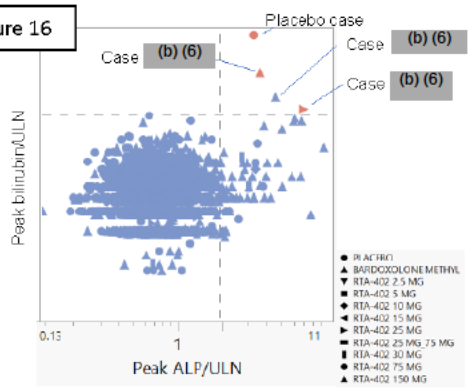
Figure 15



1340 placebo
1653 on BDX (RTA-402)

4.4.6.2 Cholestatic plot: Two cases appear in the right upper quadrants of both the eDISH and cholestatic plots which means neither met Hy's Law criteria due to peak alkaline phosphatase over 2x the ULN (Figures 15 & 16). There was one case in the right upper quadrant of the cholestatic plot that does not appear in the eDISH right upper quadrant. This case was assessed as unlikely DILI due to BDX (see Section 4.5).

Figure 16



1340 placebo
1653 on BDX (RTA-402)

4.5 Case level analysis: There were two cases on BDX treatment in Hy's Law quadrant from Analysis Set D. While evaluation data for each case is limited, neither met Hy's Law due to cholestatic injury pattern and low attribution to BDX. The third case, which appeared in the right upper quadrant of the cholestatic plot, was also assessed as unlikely DILI due to BDX.

4.5.1 Case (b) (6) (Study 402c-0903, BEACON): Possible to unlikely DILI due to BDX.

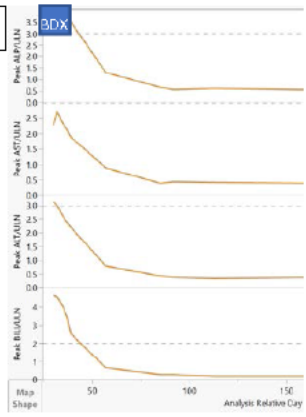
Summary: This is a 62-year-old Latinx woman with diabetes mellitus (DM) and CKD randomized to BDX treatment and had elevation in liver tests and jaundice in a cholestatic pattern about 30 days after starting BDX.

She also had hyperlipidemia and hypothyroidism. No mention of alcohol, chronic liver disease or obesity. No baseline liver tests provided in the narrative. On day 30, elevated liver enzymes and bilirubin (ALT 147, AST 84, AP 420, GGT 1005, bilirubin 5.1) were noted. These were her peak values. No symptoms mentioned; she was afebrile. Multiple gallstones were noted on imaging. BDX was stopped.

No evaluation testing provided other than the mention of gallstones. After stopping BDX, ALT, AST and bilirubin fell to normal in 27 days after presentation and peak. ALP had fallen by more than 50% by 27 days. No further labs provided.

Assessment: This case is possible DILI due to BDX. Passage of a gallstone fits as a competing diagnosis. R-value was less than 2 at onset and peak (i.e., cholestatic liver injury pattern). Therefore, this was not a Hy's Law case due to low attribution and cholestatic pattern of injury.

Figure 17



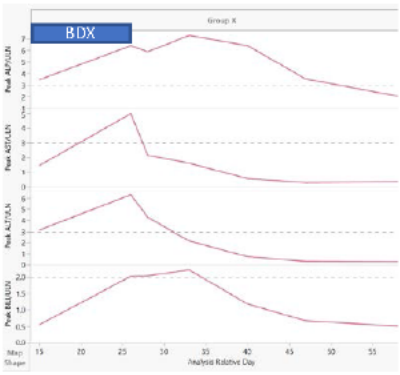
4.5.2 Case (b) (6) (Study 402-C-0801): Possible DILI due to BDX.

Summary: This is 55-year-old Caucasian woman who developed jaundice and elevated liver enzymes in a cholestatic fashion 2 weeks after starting BDX.

She had diabetes mellitus, but no mention of other medical problems. On day -14, she received cephalexin for a foot ulcer. No dosage or duration provided. No baseline liver tests provided in the narrative. On Day 25 her liver enzymes rose to ALT 163, AST 75 and ALP 362 with normal bilirubin. BDX continued but on Day 26, liver enzymes were higher, and patient became jaundiced (ALT 324, AST 246, AP 649, bilirubin 3.58. BDX was stopped, and the patient was evaluated by hepatology but no details on evaluation given. The hepatologist implicated cephalexin and not BDX.

Assessment: Assuming evaluation testing was negative, I would consider the case as probable DILI, but due to cephalexin and only possibly due to BDX. The latency is on the long side for cephalexin (14 + 25 = 39 days), but the pattern of injury (R-value <2 at onset and peak) and washout (32 days) are consistent. We are not told how long she took the cephalexin. This is not a Hy's Law case due to BDX, because of the cholestatic injury pattern and in ability to blame BDX with reasonable certainty.

Figure 18



4.5.3 Case (b) (6) (402c-0903): Unlikely DILI due to BDX.

Summary: This is 74-year-old Caucasian man who had elevation in liver enzymes in a cholestatic fashion with jaundice 8 weeks after starting BDX 20 mg/d.

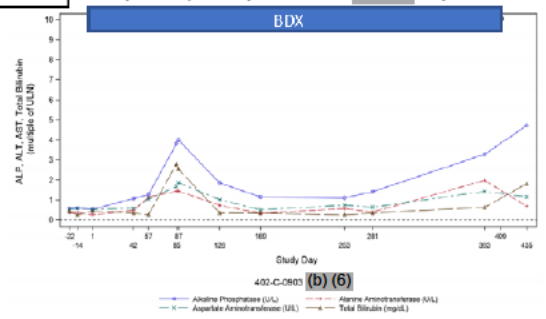
Medical history included anemia, aortic stenosis, BPH, CABG × 5, CHF class I, gallstones, hyperlipidemia, hypertension (HTN), hypothyroidism, endarterectomy, stage 4 chronic kidney disease (CKD), type 2 diabetes mellitus, thrombocytopenia. She was on multiple concomitant medications, but none compete well for this injury due to poor timing. Liver tests were normal at baseline.

On Sept 20, 2011, patient had myocardial infarction complicated by heart failure. BDX held from Sep 19 to Oct 17, 2011. On Oct 19, 2011, there was mild rise in liver enzymes which continued to ALT 54, AST 172, ALP 172 and TB of 0.3. ALP would peak at 541 and TB of 3.1. BDX was held and restarted but dates not available. No evaluation testing done. ALT, AST and TB fell to normal; ALP fell but not back to normal. Thereafter, the patient suffered 4 discreet non-liver related AE's (GI bleed, angina with hypoglycemia, hip fracture, anemia) over the next several months. Each time BDX was held and restarted but exact dates were not given. Patient finished trial on Oct 18, 2012 (Day 409) when the drug was stopped permanently.

Assessment: This is unlikely DILI due to BDX. The patient remained on BDX despite 5 interruptions in treatment. The second interruption around Day 86 was due to elevation in ALP and bilirubin, but thereafter liver enzymes settled for 250-300 days. Most of that time the patient appears to have been on BDX. Late rise of ALP is unexplained, but significant comorbidities confound

this case including the history of CHF and renal failure. The injury was cholestatic throughout. Therefore, this case would not meet Hy's Law due to low attribution and cholestatic injury. The case does not fit the pattern of transaminase induction described in Section 3.4.

Figure 19 ALT, AST, ALP, and Total Bilirubin line graph (multiples of ULN over time) IP exposure Day -22 - Day 435: Patient ID (b) (6) Study 402-C-0903



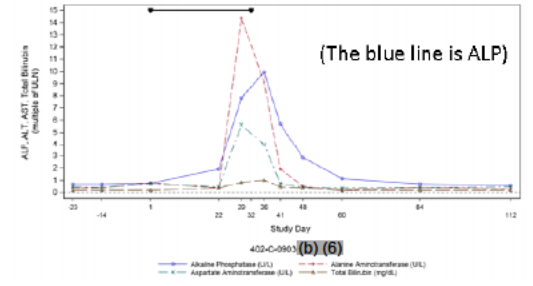
4.5.4 Cases with transaminases >10x ULN in Dataset D: We also evaluated the six cases with ALT and/or AST >10x ULN because they were outliers, potentially falling outside the explanation of off-target enzyme induction discussed in Section 3.4. One case, (b) (6) (b) (6) (Study 402-C-0903) was assessed as unlikely DILI due to BDX with gallstone disease being more likely.

One case, (b) (6) (Study 402-C-0903) was probable DILI due to BDX and had a distinctly cholestatic pattern of injury despite an ALT >10x ULN. ALP peaked at 1342 U/L. TB increased from 0.4 to 1.1 mg/dL but remained less than the ULN. The elevations resolved quickly with stopping BDX (Figure 20). This injury could be benign induction of enzymes or cholestatic injury to the liver. No biopsy was done. ALP elevations were seen in the BEACON study in a similar pattern as the ALT and AST elevations, but ALP mRNA levels were not analyzed for induction in the in vitro studies.[9]

[9] Lewis JH, et al. Clin Transl Sci, 2020

Figure 20

ALT, AST, ALP, and Total Bilirubin line graph (multiples of ULN over time)
IP exposure Day -23 - Day 112: Patient ID (b) (6) Study 402-C-0903



The other four case had transaminases attributable to BDX probably by enzyme induction. Three had rapid resolution with stopping the BDX that would be consistent with short term mRNA induction and no significant liver injury (Figures 21-23).

Figure 21

ALT, AST, ALP, and Total Bilirubin line graph (multiples of ULN over time)
IP exposure Day -19 - Day 205: Patient ID (b) (6) Study 402-C-0903

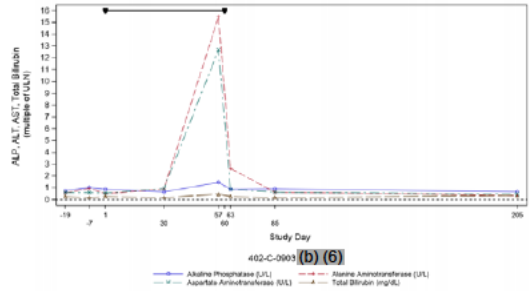


Figure 22

ALT, AST, ALP, and Total Bilirubin line graph (multiples of ULN over time)
IP exposure Day -32 - Day 717: Patient ID (b) (6) Study 402-C-1603

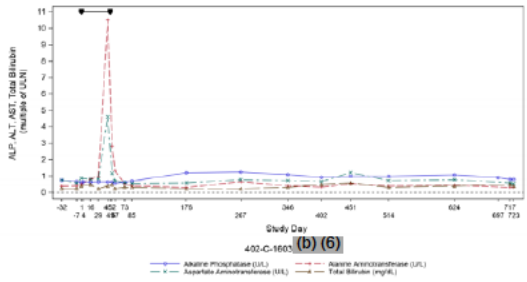
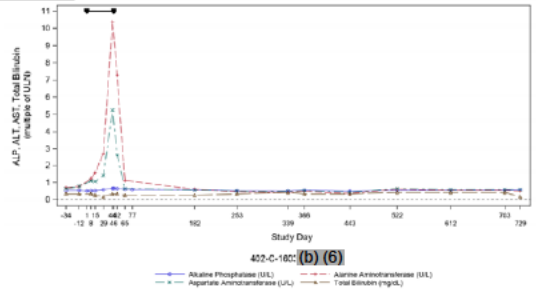
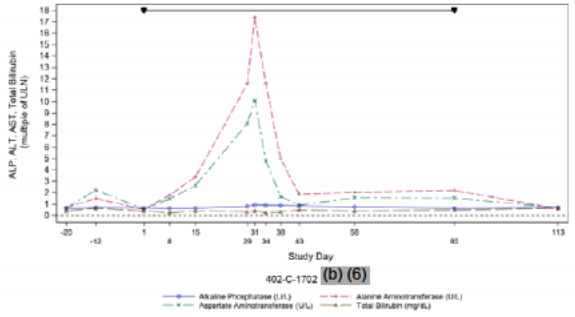


Figure 23 **ALT, AST, ALP, and Total Bilirubin line graph (multiples of ULN over time) IP exposure Day -34 - Day 729: Patient ID (b) (6) Study 402- C-1603**



One case ((b) (6) Study 402-C-1702) with ALT and AST that peaked over 10x ULN remarkably remained on BDX and is instructive. The pattern of liver injury elevation mimics that of the mean values seen in Dataset D and the BEACON study, suggesting that these outliers are likely due to mRNA induction as well (compare Figure 24 to Figures 10a & 10b in Section 4.4.1 above).

Figure 24 **ALT, AST, ALP, and Total Bilirubin line graph (multiples of ULN over time) IP exposure Day -20 - Day 113: Patient ID (b) (6) Study 402-C-1702**



5.0 Assessment and Recommendations

5.1 Assessment: Bardoxolone (BDX) is an oral small molecule that binds Keap1, which then releases Nrf2 to translocate to the nucleus where it binds promoter regions of various genes including those with antioxidant function. The sponsor hypothesizes that such gene induction mitigates kidney damage in Alport Syndrome. Nrf2 can induced many genes, and the sponsor suggests that liver enzyme gene induction explains the enzyme elevations seen.

BDX is hepatically metabolized with several metabolites produced. Two animal species (Sprague-Dawley rat, Syrian Golden hamster) were grossly intolerant of BDX with several organ toxicities and one species (Beagle dog) had severe gastrointestinal intolerance. Intolerances were so severe across

all doses for these 3 species that NOAELs could not be determined. The rat livers showed liver cysts macroscopically, biliary hyperplasia with biliary cysts and "cholangiomas" microscopically after 6 months exposure. On the other hand, BDX was well tolerated by cynomolgus monkeys exposed for 12 months and minipigs exposed for 3 months. There were no significant liver changes in these two species. Twenty-eight-day mouse studies fell in between with good liver tolerance but at lower doses only. Interestingly, matrigel-collagen sandwich culture studies suggested that BDX suppressed BSEP mRNA in rat, but induced BSEP mRNA in human hepatocytes, which could help explain the biliary changes seen in rats but not monkeys. The proposed maximum 30 mg/d dosing in this NDA is 7.6%, 1.3% and 0.1% of the NOAELs determined in mice, minipigs and monkeys, respectively, assuming an 80 kg human.

In clinical trials, there was an imbalance in liver enzyme elevations between BDX patients and placebo, but no such imbalance in bilirubin (0.1% versus 0.0%). In the largest analysis cohort (Dataset D) with 1653 exposed, the percentages with ALT elevations over 3-5x, 5-10x and >10x ULN were 4.8%, 3.3% and 0.3% respectively versus 0.2%, 0.2% and 0% for placebo (n=1340). For alkaline phosphatase, percent with elevations >3x ULN was 1.4% on BDX versus 0.2% on placebo. There were two cases falling in Hy's Law quadrant on eDISH, but case level analyses suggest, at most, possible attribution to BDX. Gallstone disease and another medication were plausible competing diagnoses. Moreover, both had cholestatic liver injuries thus not meeting Hy's Law. One case fell in the right upper quadrant of the cholestatic plot (i.e., jaundice with AP >2x ULN), and this case was assessed as unlikely due to BDX with congestive hepatopathy (heart failure) competing.

The sponsor's in vitro studies suggest an interesting off-target, benign liver enzyme induction.[10] We agree with this hypothesis because the in vitro studies appear well-done, and the liver enzyme course with rapid dechallenge and no bilirubin elevation would be consistent with mRNA induction. We found no other sources of liver enzyme elevation (e.g., muscle injury, hemolysis). The enzyme elevation patterns were similar in the diabetic nephropathy and AS studies.

Thus, there were no Hy's Law cases or cholestatic injury cases with jaundice attributable to BDX. Indeed, it is arguable that the liver enzyme elevations would have had no histologically confirmed liver injury had biopsies been done. Transaminase elevations were typically modest (<3-5x ULN), fell with continued drug use and quickly resolved to normal upon holding BDX (Figures 8, 10, 11). These characteristics were also seen for the outliers with transaminases over 10x ULN, which would be consistent with benign gene induction.

[10] Lewis JH, et al. Clin Transl Sci (2020)

In summary, we do not see a liver injury that should hold up approval of this drug. However, elevation in liver enzymes will be seen post-marketing and language addressing such elevations will be needed in the labeling should BDX be approved (see recommendations in Section 5.2). Hepatic impairment studies suggest significantly higher exposure in those with moderate to severe hepatic impairment, so use in patients with such severe impairment should be done with caution. We expect the prevalence of advanced cirrhosis to be low in this younger AS population.

5.2 Recommendations:

a) Do not hold up approval for the liver enzyme elevations seen in this NDA.
b) If BDX is approved, labeling should include information about liver enzyme elevations in warnings and precautions. Please consult the DILI Team should you need help with wording.
c) BDX should be used with caution in patients with cirrhosis and moderate to severe hepatic impairment.

Paul H. Hayashi -S

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