24 February 2022
EMA/913943/2022
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Imbarkyd

International non-proprietary name: bardoxolone methyl

Procedure No. EMEA/H/C/005869/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of Contents

Table of Contents **2**
List of abbreviations **4**
1. CHMP Recommendations **8**
1.1. Questions to be posed to additional experts 9
1.2. Inspection issues 10
1.2.1. GMP inspection(s) 10
1.2.2. GCP inspection(s) 10
1.3. New active substance status 10
1.4. Additional data exclusivity /Marketing protection 10
1.5. Similarity with authorised orphan medicinal products 10
1.6. Derogation(s) from market exclusivity 10
2. Executive summary **10**
2.1. Problem statement 10
2.1.1. Disease or condition 10
2.1.2. Epidemiology 11
2.1.3. Aetiology and pathogenesis 11
2.1.4. Clinical presentation and diagnosis 11
2.1.5. Management 11
2.2. About the product 12
2.3. The development programme/compliance with guidance/scientific advice 12
2.4. General comments on compliance with GMP, GLP, GCP 13
2.5. Type of application and other comments on the submitted dossier 13
2.5.1. Legal basis 13
2.5.2. New active substance status 13
2.5.3. Orphan designation 13
2.5.4. Similarity with orphan medicinal products 14
2.5.5. Information on paediatric requirements 14
3. Scientific overview and discussion **14**
3.1. Quality aspects 14
3.1.1. Introduction 14
3.1.2. Active Substance 14
3.1.3. Finished Medicinal Product 17
3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects 20
3.2. Non-clinical aspects 21
3.2.1. Introduction 21
3.2.2. Pharmacology 22
3.2.3. Pharmacokinetics 29
3.2.4. Toxicology 33
3.2.5. Ecotoxicity/environmental risk assessment 45
3.2.6. Discussion on non-clinical aspects 45
3.2.7. Conclusion on non-clinical aspects 56
3.3. Clinical aspects 57
3.3.1. Clinical pharmacology 59

3.3.2. Discussion on clinical pharmacology 74
Pharmacokinetics 74
Pharmacodynamics 80
3.3.3. Conclusions on clinical pharmacology 81
Pharmacokinetics 81
Pharmacodynamics 81
3.3.4. Clinical efficacy 82
3.3.5. Discussion on clinical efficacy 124
3.3.6. Conclusions on clinical efficacy 133
3.3.7. Clinical safety 133
3.3.8. Discussion on clinical safety 170
3.3.9. Conclusions on clinical safety 176
3.4. Risk management plan 177
3.4.1. Safety Specification 177
3.4.2. Pharmacovigilance plan 179
3.4.3. Risk minimisation measures 181
3.4.4. Conclusion on the RMP 183
3.5. Pharmacovigilance 183
3.5.1. Pharmacovigilance system 183
3.5.2. Periodic Safety Update Reports submission requirements 183
4. Non-Conformity with agreed Paediatric Investigation Plan 183
5. Benefit risk assessment 183
5.1. Therapeutic Context 183
5.1.1. Disease or condition 183
5.1.2. Available therapies and unmet medical need 184
5.1.3. Main clinical studies 184
5.2. Favourable effects 184
5.3. Uncertainties and limitations about favourable effects 187
5.4. Unfavourable effects 189
5.5. Uncertainties and limitations about unfavourable effects 191
5.6. Effects Table 193
5.7. Benefit-risk assessment and discussion 195
5.7.1. Importance of favourable and unfavourable effects 195
5.7.2. Balance of benefits and risks 197
5.7.3. Additional considerations on the benefit-risk balance 197
5.8. Conclusions 198

List of abbreviations

ΔeGFR	change from baseline in estimated glomerular filtration rate
AASK	African American Study of Kidney Disease and Hypertension
ACEi	Angiotensin-converting enzyme inhibitor
ADAS	Autosomal dominant Alport syndrome
ADPKD	Autosomal dominant polycystic kidney disease
ADR	Adverse drug reactions
AE	Adverse event
AI	American Indian or Alaska Native
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ARAS	Autosomal recessive Alport syndrome
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BARD	bardoxolone methyl
BCRP	Breast cancer resistance protein
BMI	Body mass index
BNP	B-type natriuretic peptide or brain natriuretic peptide
BUN	Blood urea nitrogen
CDC	Centers for Disease Control and Prevention
CGI-I	Clinical Global Impression – Improvement
CHF	Congestive heart failure
CI	Confidence interval
CK	Creatine kinase
CKD	Chronic kidney disease
CKD-PC	Chronic Kidney Disease Prognosis Consortium
CrCl	Creatinine clearance
CSR	Clinical study report
CTD	Common Technical Document
CV	cardiovascular
DBL	database lock
DBP	Diastolic blood pressure
DCAE	Discontinuation due to adverse event
DCO	Data cut-off
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
DTPA	Diethylenetriaminepentaacetic acid
EASL	European Association for the Study of the Liver
ECH	Echocardiogram
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity

EC	Ethics committee
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
eGFRo	Estimated glomerular filtration rate, baseline status
EMA	European Medicines Agency
EOT	end of trial
ESKD	End-stage kidney disease
ESRD	End stage renal disease
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
F1	Relative bioavailability
FDA	Food and Drug Administration
FSGS	Focal segmental glomerulosclerosis
FU	follow-up
GBM	Glomerular basement membrane
GFR	Glomerular filtration rate
GCLM	Glutamate-cysteine ligase, modifier subunit
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMR	Geometric mean ratio
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GSH	Glutathione
HR	Hazard ratio
HUI	Health utilities index
ICH	International Council for Harmonisation
IgAN	Immunoglobulin A nephropathy
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ISS	Integrated summary of safety
ITT	Intent-to-treat
Keap1	Kelch-like ECH-associated protein 1
KPROG	Rate of disease progression
LSM	Least square mean
MAA	Marketing Authorization Application
MACE	Major adverse cardiac events
MCP-1	Monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mITT	Modified intent-to-treat
MMRM	Mixed model repeated measures
MPA	Medical Products Agency
NA	not applicable
NADPH	Nicotinamide adenine dinucleotide phosphate hydrogen

NCT	National Clinical Trial
NDA	New drug application
NF-κB	Nuclear factor-kappa B
NKF	National Kidney Foundation
NH	Native Hawaiian or Other Pacific Islander
Nrf2	Nuclear factor-erythroid 2-related factor 2
NYHA	New York Heart Association classification of heart failure
ODD	Orphan Drug Designation
P-gp	P-glycoprotein
PBO	Placebo
PD	Pharmacodynamic(s)
PDCO	Paediatric Committee
PGIC	Patient Global Impression of Change
PH	Pulmonary hypertension
PI	Principal Investigator
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
PopPK	Population PK
PP	Per Protocol
PPI	Proton-pump inhibitor
PRAC	Pharmacovigilance Risk Assessment Committee
PSM	Pre-submission meeting
QD	Once daily
QoL	Quality of life
QT/QTc	QT interval/ corrected QT
ΔΔQTcF	QT interval with Fridericia's correction
ΔΔQTcI	Individual-specific correction
RAAS	Renin angiotensin aldosterone system
ROS	Reactive oxygen species
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SCS	Summary of clinical safety
SD	Standard deviation
SDD	Spray-dried dispersion
SEM	Standard error of the measure
SMQ	Standardized MedDRA Query
SNGFR	Single nephron glomerular filtration rate
SOC	System organ class
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
TGF-β	Transforming growth factor beta

TNF	Tumour necrosis factor
TQT	Thorough QT
UACR	Urinary albumin-to-creatinine ratio
ULN	Upper limit of normal
US	United States
XLAS	X-linked Alport syndrome

1. CHMP Recommendations

Based on the review of the data on quality, safety, efficacy, the application for Imbarkyd in the treatment of chronic kidney disease (CKD) caused by Alport syndrome in adults and adolescents aged 12 years and above is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions (see section VI).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

- Quality:
  - Additional justification of the starting material proposed for the GMP-synthesis is required.
  - The nitrosamines risk evaluation is not yet considered acceptable and additional information/data is required.
- Cross disciplinary (Non-clinical, pharmacokinetics)
  - The metabolism of bardoxolone methyl is not sufficiently described, and it is unclear if there are additional major and/or active plasma metabolites that need further preclinical, pharmacological or pharmacokinetic characterisation.
- Indication; B/R:
  - The proposed indication is broad and includes all stages of renal function in Alport syndrome. It is however questioned that a positive benefit/risk ratio has been shown for the entire target population
    i. The applicant is requested to justify the use of bardoxolone in subjects with severe renal disease corresponding to CKD 4-5 or to reflect the limitations of the study population in the wording of the indication
    ii. The applicant is requested to justify the extrapolation of efficacy data from the study population consisting of subjects with CKD 2-3b to subjects with CKD 4-5, or to reflect the limitations of the study population in the wording of the indication.
- Clinical efficacy and safety:

1. The benefit of bardoxolone in the treatment of Alport syndrome needs further justification.
   a. The results of the phase 3 study (1603) indicate that eGFR increased rapidly compared to baseline during the first approximately 12 weeks with a subsequent reduction of eGFR from 12 to Week 48 at a rate visually not differing from that in the placebo arm. The long-term benefit of the observed rapid pharmacodynamic effect should be further justified including (but not limited to) a thorough scientific discussion based on available literature, including non-clinical data. In specific, the applicant should justify that long-term Nrf2 activation – or other bardoxolone- mediated effects- does not have a negative impact on kidney function over time. In this context, the findings of renal toxicity in mice should be taken into account as well as the possibility that the acute PD-effect could be caused by increased intraglomerular pressure.

b. During the off-treatment period, a rather rapid decline in eGFR was noted. In this context, possible rebound effects upon treatment cessation should be discussed considering that the off-treatment period may have been too short to document such an effect.

c. Bardoxolone treatment was related to an increase in the urine albumin creatinine ratio (UACR) which is a major concern considering that albumin excretion is a well described surrogate marker for glomerular damage and in general related, amongst others factors, to an increased glomerular pressure.
The applicant should discuss the possibility of a direct effect of bardoxolone on the podocytes resulting in an alteration in the filtration barrier, and the potential involvement of an increased glomerular pressure. Percent changes from baseline UACR to week 12, 48 and week 100 should be provided for both treatment arms supplementing the analyses already submitted. Furthermore, the time dependency of UACR increase and persistence of UACR increase upon bardoxolone treatment interruption should also be discussed**.**

d. Considering the uncertainties reflected above, the applicant should present further long-term data as available with specific focus on the possibility of detrimental long-term effects of treatment. The applicant should also discuss how further adequate long-term data could be provided. In this context, it should also be considered that the continuation Study 1803 (EAGLE) is biased towards responders. Furthermore, Study 1803 is uncontrolled, which hampers the assessment of potential detrimental long-term effect of treatment in the Study.

- Study conduct:
    - Concerns about study conduct in light of unblinding of the Sponsor midway through the trial, poor communication with stakeholders during the trial, failure to re-consent patients, communication with Data Monitoring Committee, extensive protocol changes and frequent major protocol deviations including the informed consent need to be further addressed
- Clinical safety:
    - The previous BEACON study with bardoxolone was terminated early due to an increase in heart failure events associated with fluid retention. In the present Alport population with lower cardiovascular risk, no cases of heart failure occurred, but cases of increased BNP levels and peripheral oedema were more frequent in the bardoxolone group. Considering that bardoxolone is intended for potential lifelong treatment, it is critical to define a safe target population, taking into account that cardiovascular risk factors increase over time. Additional justification is requested. Subjects with NYHA III-IV were excluded from the pivotal study to reduce the potential for fluid overload; however, the applicant proposes a contraindication for subjects with NYHA IV only. The applicant should justify the safe use of bardoxolone in subjects with NYHA III or include these subjects in the contraindication. Based on the mechanism of action and the adverse events observed in the Alport studies, the applicant should also discuss if additional contraindications/precautions should be applied.

1.1. Questions to be posed to additional experts

Not applicable at this time point

1.2. Inspection issues

1.2.1. GMP inspection(s)

There is no proposal from the CHMP

1.2.2. GCP inspection(s)

No GCP inspection is required by the CHMP at this time point.

1.3. New active substance status

Based on the review of the data, it is considered that the active substance bardoxolone methyl contained in the medicinal product Imbarkyd could be qualified as a new active substance provided that satisfactory responses are given to the concerns (major objection) as detailed in the List of Questions.

1.4. Additional data exclusivity /Marketing protection

N/A

1.5. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application did not submit a critical report, addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

According to the Community Register of Orphan Medicinal Products for Human Use (COMP), two other medicinal products currently have orphan medicinal product designation for the treatment of Alport Syndrome. Neither has been granted a marketing authorisation at this time point. It is therefore agreed that at this time point, no similarity report is warranted. However, this may have to be reassessed during the procedure.

1.6. Derogation(s) from market exclusivity

N/A

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

Alport syndrome is an inherited progressive form of glomerular disease, often associated with sensorineural hearing loss and ocular abnormalities.

The proposed indication for Imbarkyd is *treatment of chronic kidney disease (CKD) caused by Alport syndrome in adults and adolescents aged 12 years and above*.

2.1.2. Epidemiology

While the global prevalence of Alport syndrome is not known, studies in the EU indicate that Alport syndrome is observed in approximately 1:50,000 live births and that X-linked disease among males is observed in 1:17,000 live births. Another study in the EU estimated the prevalence as 1 in 25,000.

Although Alport syndrome is a rare condition, it is the second most common genetic cause of kidney failure and accounts for 1% to 2% of patients who reach end stage renal disease (ESRD) in Europe and for >1% of patients who receive renal replacement therapy.

2.1.3. Aetiology and pathogenesis

Alport syndrome is caused by mutations in genes encoding the α3, α4, and α5 chains of Type IV collagen, which is a major constituent of the glomerular basement membrane (GBM) in the kidney. The defective Type IV collagen leads to splitting in the GBM and loss of integrity, triggering abnormal leakage of proteins (e.g., albumin) and excessive protein reabsorption in the proximal tubules, resulting in glomerulosclerosis and tubulo-interstitial fibrosis. The different mutations result in different inheritance pattern.

Transmission of Alport syndrome can be X-linked, autosomal recessive, or autosomal dominant, depending on the affected gene(s). The most common form of Alport Syndrome is the X-linked form, representing roughly 55-70% of all cases.

2.1.4. Clinical presentation and diagnosis

Alport syndrome is a progressive renal disorder, leading to chronic kidney disease (CKD) and development of ESRD. Alport nephropathy progresses through a consistent set of milestones, beginning with isolated haematuria, followed by moderate albuminuria, severe proteinuria, hypertension and decline in glomerular filtration rate (GFR). Symptoms from progressive CKD caused by Alport syndrome is not different from that of other causes; however, as Alport syndrome may lead to ESRD at a relatively young age, a negative impact on work, school and everyday life is often reported.

The severity of disease differs by the inheritance pattern and the nature of the causative mutation. As per data from National Organization for Rare Disorders/Alport Syndrome Foundation, approximately 50% of untreated males with X-linked Alport syndrome (XLAS) develop kidney failure by age 25. The lifetime risk for ESRD in male subjects with XLAS is 100% compared to 25% in female subjects. The lifetime risk for ESRD for both males and females is 100% in autosomal recessive (ARAS) and 20% in autosomal dominant (ADAS)

In addition to the kidney involvement, bilateral sensorineural hearing loss and eye abnormalities are among the clinical manifestations of Alport syndrome.

The diagnosis of Alport syndrome is preferentially made by molecular genetic testing.

2.1.5. Management

Currently, there are no therapies specifically approved for the treatment of Alport syndrome. The current goals of treatment include monitoring progression of the disease and treating with available therapeutics labelled for other indications.

Current treatment recommendations for the decline of kidney function in patients with Alport syndrome include treatment with inhibitors of the RAAS pathway (e.g., ACEi and/or ARBs) in patients with Alport syndrome and proteinuria. Bardoxolone methyl has been administered both with and without RAAS

inhibition in the Alport studies, and is not intended as an alternative treatment, but a complement to RAAS inhibition

2.2. About the product

Bardoxolone methyl is an orally bioavailable activator of the transcription factor Nuclear factor erythroid 2-related factor 2 (Nrf2) activator. Bardoxolone activates the Keap1-Nrf2 pathway by binding to Keap1, leading to Nrf2 activation by preventing degradation of Nrf2.

Nrf2 is a transcription factor that translocates to the nucleus and binds to highly specific promoter regions of DNA called antioxidant response elements (AREs), which subsequently leads to transcriptional induction of hundreds of target genes associated with e.g., inflammation, cancer, neurodegenerative diseases, and other major diseases (Ahmed et al; BBA-Mol Basis Dis, 2017; https://doi.org/10.1016/j.bbadis.2016.11.005).

As part of the inflammatory response, cells may temporarily alter their metabolic state by suppressing mitochondrial adenosine triphosphate (ATP) production in favour of producing reactive oxygen species (ROS) that enhance and propagate the inflammatory response and directly target the harmful stimulus. The Keap1-Nrf2 pathway plays a key role in the resolution phase of inflammation by regulating the expression of genes involved in redox balance.

The validation of Nrf2 as a relevant therapeutic target for kidney diseases is supported by peer-reviewed manuscripts that characterise its effects in transgenic animals that are missing Nrf2 (Nrf2-knockout) or have constitutive activation of Nrf2 (through genetic knockdown of Keap1). Genetic research data in humans demonstrate that the Keap1-Nrf2 pathway is suppressed in many forms of CKD, including Alport syndrome, and is an important correlate with GFR (Martini et al; J Am Soc Nephrol 2014;25:2559-72).

The proposed posology is dependent on baseline urinary albumin/creatinine ratio (UACR). The proposed starting dose is 5 mg once daily during the first 2 weeks for subjects >18 years and 5 mg every other day during the first week, then 5 mg once daily during the second week for subjects aged ≥ 12 years to < 18 years. Dosing is increased during the first eight weeks of treatment to a target dose of 20 mg (baseline UACR ≤300 mg/g) or 30 mg (UACR >300 mg/g once daily for both adults and adolescents.

2.3. The development programme/compliance with guidance/scientific advice

The initial clinical development of bardoxolone methyl began in 2005 in the field of oncology. In clinical studies in patients with cancer, increases in eGFR were noted. Based on this unexpected finding, the Sponsor started a development program for CKD. Results from these studies suggested that bardoxolone methyl had the potential to slow the irreversible loss of kidney function in multiple types of CKD. However, an increased risk for fluid overload was observed in a subset of patients with type 2 diabetes and Stage 4 CKD in the large phase 3 BEACON study (Study 402-C-0903), leading to premature termination of the study for safety reasons. Post-hoc analysis from this study identified two risk factors as significant predictors of fluid overload events, namely elevated baseline B-type natriuretic peptide or brain natriuretic peptide (BNP) (i.e., >200 pg/mL) and prior hospitalisation for heart failure. As a result, all subsequent studies, including those conducted in patients with Alport syndrome, excluded patients with these clinical characteristics as part of a broader strategy to mitigate the potential risk for fluid overload that may occur with bardoxolone methyl.

Protocol assistance was obtained from EMA September 2018 (EMA/CHMP/SAWP/599796/2018) for Study 1603 Phase 3. For details, please refer to the Clinical AR.

In general, the applicant has taken the advice from CHMP guidance into consideration or provided an acceptable justification for not doing so. Major points were the timing and definition of the primary endpoint. The primary endpoint was amended with an additional primary analysis at Week 100 to meet the CHMP's note that the primary analysis at Week 48 may be too early and carries a risk of overestimating the benefit of the compound. As for the CHMP's recommendation that primary efficacy endpoint should be timed to a predefined and justified loss in GFR, such as 50%, the applicant has referred to the importance of total eGFR slope highlighted in NKF sponsored workshop conducted in collaboration with the FDA and EMA 2018. This is accepted.

Adolescents from the age of 12 years were eligible for the Alport development program.

The applicant also received Scientific Advice (SA) from EMA CHMP on October 21, 2010 (EMA/CHMP/SAWP/620628/2010) and on September 20, 2018 (EMA/CHMP/SAWP/599796/2018) regarding quality. Based on the provided data and MAH questions, the CHMP gave advice in 2010 on selection of starting materials, stability package for the drug substance, drug product intermediate and finished product as well as drug product shelf life. Considering the introduction of ICH Q11 in 2012, the advice on selection of starting materials is requested again in 2018 together with the advice on the proposed specifications for the drug substance, drug product intermediate and finished product, manufacturing process validation as well as stability data for drug product intermediate (holding time) and drug product shelf life.

2.4. General comments on compliance with GMP, GLP, GCP

No concerns have been raised during the assessment of the Quality part that would give cause of any GMP inspection prior to authorisation.

All pivotal non-clinical studies were performed in compliance with GLP.

No concerns have been raised during the assessment of the Clinical part that would give cause of any GCP inspection at this time point.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

2.5.2. New active substance status

The applicant requested the active substance bardoxolone methyl contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Assessment of this claim is appended.

2.5.3. Orphan designation

Imbarkyd was designated as an orphan medicinal product EU/3/18/2019 on 2018-05-25 in the following condition: treatment of Alport syndrome.

2.5.4. Similarity with orphan medicinal products

The application contained a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products.

The MAH concluded that bardoxolone methyl is not similar to any other authorised orphan medicinal product in the EU. This conclusion can be agreed on. As there are no other orphan medicinal products authorised in the claimed indication a similarity assessment is not applicable.

2.5.5. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0280/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0280/2021 was not yet completed as some measures were deferred.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as hard capsules containing 5 mg or 15 mg of bardoxolone methyl as active substance.

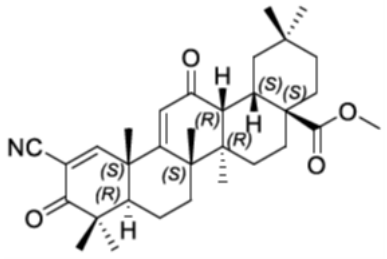
Other ingredients are: methacrylic acid-ethyl acrylate copolymer, lactose monohydrate, silicified microcrystalline cellulose (microcrystalline cellulose and silica colloidal anhydrous), hypromellose, sodium laurilsulfate, silica colloidal anhydrous, magnesium stearate, gelatin, titanium dioxide, brilliant blue FCF, erythrosine, black iron oxide, potassium hydroxide, propylene glycol and shellac.

The applicant states that the drug product is packaged in white polyvinylchloride (PVC)/polyvinylidene chloride (PVdC)//aluminium blister packages (please see point raised related to drug product packaging description).

3.1.2. Active Substance

3.1.2.1. General Information

Bardoxolone methyl (INNM, USAN).



Bardoxolone methyl

Molecular formula: $C_{32}H_{43}NO_4$
Molecular mass: 505.70

No CEP is available for bardoxolone methyl and the ASMF procedure is not used. The full information presented in the dossier is used as basis for assessment of the active substance in this application.

3.1.2.2. Manufacture, process controls and characterisation

The drug substance bardoxolone methyl is obtained from a single GMP compliant source.

The description of the proposed GMP-synthesis process and the in-process applied seem acceptable. However, additional clarification regarding the proposed reprocessing is requested, and the GMP starting material has not yet been sufficiently justified. A final decision on the acceptability of the description and in-process controls will be taken when the choice of starting material has been sufficiently justified (major objection).

The specification are presented for the proposed starting material. The justifications for the specifications for EA01020 seem reasonable, but, the specification is not considered fully acceptable until the choice of EA01020 as GMP-starting material has been fully justified. Batch analysis data for EA01020 complying with the proposed specification is presented. The applicant's assessment of the risk for presence of N-nitrosamines in the proposed starting material EA01020 as very low based on the risk analyses presented by the EA01020 manufacturers is endorsed.

The control of reagents, solvents, and auxiliary materials used in the synthesis of the drug substance will be considered acceptable when the choice of EA01020 as GMP-starting material has been fully justified as requested above. However, If the starting point for the GMP-synthesis changes for some reason, additional materials may need to be controlled.

Critical process parameters and critical in-process controls in the manufacture of the drug substance are discussed and justified. Results for batches tested for these critical process parameters and critical in-process controls are presented. The specification are presented for the proposed intermediate EA01030. Analysis results for batches of EA01030 are presented. The control of critical steps and intermediates in the synthesis of the drug substance will be considered acceptable when the choice of EA01020 as GMP-starting material has been fully justified.

The description of the manufacturing process development, which addresses the manufacturing process history and differences between the different processes (A, B, C, D, E and F; with F being the current process) used for manufacture of the drug substance, differences in the HPLC method used for determination of residual solvents, results from spiking studies, continuing process improvements, a risk assessment of the process, and discussion of proven acceptable ranges and control strategy development. The description of the manufacturing process development is considered comprehensive and acceptable.

The characterization of the drug substance includes a structural characterization by different standard techniques and a discussion regarding polymorphism and characterization of and solubility for the major forms. However, the results of optical rotation measured on several API batches should be additionally enclosed for the confirmation that a single stereoisomer of bardoxolone methyl is repeatedly produced by the applied manufacturing process.

The formation, control, and qualification of related substances are discussed in the impurities section of the dossier. Additional clarifications regarding the proposed control strategy considering impurities controlled as unspecified impurities in the drug substance is needed. A photodegradation product formed under forced degradation conditions is also discussed. Related substances are assessed for mutagenic potential according to ICH M7 and are classified as Class 4 or Class 5 compounds, and therefore treated as non-mutagenic impurities. In addition, all substances used in the active substance manufacturing process should be evaluated according to ICH M7. In addition, if the starting point in

the GMP-synthesis is redefined, additional impurity information regarding an extended GMP-process may be necessary.

The information presented regarding residual solvents present in the drug substance, which are controlled in accordance with ICH Q3C, is considered acceptable. The information presented regarding elemental impurities is considered acceptable, and all relevant elements are below their respective Option 1 limits (ICH Q3D) in both the proposed starting material and in the drug substance. The nitrosamine risk assessment presented for the drug substance is considered sufficient. The risk assessment confirms that risk of N-nitrosamine formation in the manufacturing process is very low due to the very low content of nitrosating agents available. However, the applicant has been requested to provide additional comments.

3.1.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

The drug substance specification contains tests typical for this type of active substance. The validation data presented for these analytical methods are acceptable in most parts, but additional data need to be presented for some methods. In addition, clarification regarding the control strategy used for the impurities that are not sufficiently separated by the applied related substances method is requested.

Batch analysis data are presented for drug substance batches manufactured in less than commercial scale that were used in pharmacology/toxicology studies and/or were used to produce drug product that was used in clinical studies (and development stability), and for commercial scale batches used in process validation, primary stability studies, and for manufacture of drug product used in clinical studies. The batch analysis data presented for the commercial batches comply with respect to all parameters included in the proposed drug substance specification. The batch analysis data presented for batches manufactured by previous synthesis routes at less than commercial scale were tested against previous specification requirements, mainly regarding impurities and residual solvents. The information presented regarding the drug substance batches produced and the batch analysis data presented for these batches are considered acceptable.

The justifications for the drug substance specifications are acceptable except regarding the justification of certain impurities for which additional information is requested. In addition, inclusion of optical rotation in the drug substance specification testing is requested.

The information presented regarding reference standards or materials is not considered acceptable. A document which addresses process validation has erroneously been placed in section 3.2.S.5 of the dossier instead of the correct documentation. The applicant has been requested to present the correct information in this dossier.

The container closure system for the drug substance, which is the same as used in the primary stability studies, is sufficiently described, complies with relevant requirements for plastic materials intended to come into contact with food stuffs, and seems suitable for its intended purpose.

The container closure for in-process material during drug substance manufacture is also sufficiently described, complies with relevant requirements for plastic materials intended to come into contact with food stuffs, and seems suitable for its intended purpose.

3.1.2.4. Stability

Stability study data from storage, all at commercial scale in the proposed commercial package, are presented. In addition, photostability stability studies of the drug substance in accordance with ICH Q1B has been performed. Data from forced degradation studies under various stress conditions (thermal, acidic, alkaline, oxidative and photolytic) are also presented. The analysis methods used

were the same as for routine analysis. The stability results presented show that the drug substance does not degrade under long-term, accelerated, and photo stability studies in accordance with ICH and that the requested shelf-life without any special storage conditions is acceptable. The forced degradation stability data presented for the drug substance, which show that the analysis methods used are stability indicating, are considered sufficient.

3.1.3. Finished Medicinal Product

3.1.3.1. Description of the product and Pharmaceutical Development

Description of the Product

Imbarkyd capsules are manufactured from a common blend formulation in the two strengths 5 mg and 15 mg.

Descriptions:

5 mg capsule:	Light blue body and blue cap, opaque capsules, imprinted with "RTA 402" in black ink on the body and "5" on the cap in white ink. Capsule length approximately 14 mm and diameter approximately 5 mm (size 4).
15 mg capsule:	White body and blue cap, opaque capsules, imprinted with "RTA 402" in black ink on the body and "15" on the cap in white ink. Capsule length approximately 19 mm and diameter approximately 7 mm (size 1).

The composition of Imbarkyd capsules is presented in the tables below.

The qualitative compositions of the inks used for printing the capsule shells are provided in the tables below. Only trace amounts of the edible inks are present in the final dosage forms.

The information provided with respect to the description and composition of the drug product is generally acceptable. However, additional information related to quality standards and grade designations of the excipients has been requested from the applicant.

The applicant is also asked to provide additional discussion in section 3.2.P.4 regarding the functionality related characteristics of the excipients used.

Pharmaceutical Development

The development of the drug product is well described and the applicant has presented the Target Product Profile and Critical Quality Attributes of the drug product have been identified. However, a number of questions are posed, mainly regarding the design of experiments (DoE) studies performed and proven acceptable ranges (PARs) of process parameters listed. The information about the DoE studies and the evaluation of the same is not considered sufficient to facilitate assessment or to justify any claimed PARs/Design spaces. See also below.

The applicant's selection and the function of key excipients have been discussed.

The drug product manufacturing process consists of typical manufacturing operations for this type of product.

The conclusions that process parameter levels applied during development and for confirmatory batches are suitable for full-scale manufacturing are generally found reasonable based on data provided. Likewise, the conclusion drawn that the proposed process parameters are suitable for manufacturing capsules compliant with the drug product specifications may be true. However, in most cases the design of the experiments is not clearly described, nor are models or their power. Hence the

question mentioned above with respect to the description and evaluation of the DoE studies and the claimed PARs of process parameters. An additional question has also been raised related to criticality classification and proposed ranges for individual process parameters.

The pivotal Alport syndrome clinical studies 402-C-1603 and 402-C-1803 in this application have been performed using the proposed commercial formulation (with the exception of capsule shell colorants). The statement that the manufacturing process applied for bardoxolone methyl capsules registration/ primary stability batches is representative of the one for commercial production is reasonable based on comparative data provided.

The development of the dissolution test method has been discussed by the applicant, however additional information is requested.

The discriminatory properties of the proposed dissolution method may be considered acceptable, provided that the dissolution specification is appropriately tightened (please see the question raised regarding the proposed specification limit).

The suitability and safety of the proposed formulation for the paediatric population has not been discussed.

Based on development and stability studies, the chosen packaging materials for the drug product are considered adequate to support the stability and use of the product.

3.1.3.2. Manufacture of the product and process controls

Manufacture and Process Controls

The manufacturing and controls of Imbarkyd capsules are conducted at the facilities listed in the table below.

The drug product manufacturing process and process controls have been acceptably described in flow diagrams and narratives with indication of the critical steps. The critical steps, critical in-process controls and critical process parameters (CPPs) for the manufacture have been established during the development and scale up of the unit operations for the proposed commercial process. The in-process controls applied are considered appropriate. However, the proposed PARs/Design spaces are not yet considered acceptably justified. See above under pharmaceutical development regarding this issue.

Also refer to the ´Stability of the product´ subsection below.

Confirmation that the shelf life of the product is calculated according to the Note for Guidance on Start of Shelf-Life of the Finished Dosage Form (CPMP/QWP/072/96) is requested.

Process validation / verification

Manufacturing process validation data from PPQ (process performance qualification) batches has been provided. Commercial-scale batches were manufactured and studied. The blend batches were divided in two parts which were encapsulated to give final drug product of the two strengths. The resulting PPQ batches are also used in stability studies (commitment stability batches). The process validation activities´ results indicate that the manufacturing process is capable to consistently produce drug products of adequate quality.

3.1.3.3. Product specification, analytical procedures, batch analysis

Specifications

The proposed Imbarkyd capsules´ specifications are presented.

Adequate specification parameters have been included in the drug product specifications, although not all acceptance criteria are found acceptable. Potential impurities in the drug product are generally acceptably discussed. The proposed wider shelf-life assay limits are not considered acceptably justified. Likewise, the proposed dissolution specification limit is not deemed sufficiently justified. The limit for the specified impurity is in accordance with the ICH Q3B qualification threshold and hence accepted as is the limit for unspecified degradation products (in line with the ICH Q3B identification threshold). The Total degradation products´ limit is also considered acceptable. However, the acceptability of the proposed limit, which is above the ICH Q3B qualification threshold, is pending. A question regarding this is posed in the drug substance part.

The nitrosamines risk evaluation is not yet considered acceptable and additional information/data is required. Hence, a **Major objection** is raised.

Analytical procedures and reference standards

The analytical procedures have generally been acceptably described and validated. However, additional data related to the performed forced degradation study are requested to confirm the stability indicating power of the proposed analytical methods for assay and related substances.

Beyond the reference standards used for testing the drug substance, there are no additional reference standards (quantitative or qualitative) used to test and release the drug product. Reference to the drug substance part regarding reference standards is considered acceptable. However, a question is raised in the drug substance part since information is missing.

Batch analysis

Batch analysis results for three registration batches of each of the capsule strengths confirm consistency and uniformity of the product and indicate that the manufacturing process is under control. Blends for the registration batches were manufactured at a scale of at least one tenth of the proposed commercial scale. The final blend for each drug product registration stability batch was encapsulated into the 5-mg and 15-mg commercial strengths.

It is noted that the batch numbers of the clinical batches listed in section 3.2.P.5.4 do not match with the batch numbers listed in the respective clinical study reports (Module 5), clarification is therefore requested.

Container closure

It is noted that the general description of the drug product primary packaging (white PVC/PVdC//Alu blisters) is not in line with the detailed packaging description (white PVC/PE/PVdC/PE/PVC//Alu blisters). The applicant is asked to confirm that the intended drug product packaging is the white PVC/PE/PVdC/PE/PVC//Alu blister and to update all the relevant sections of Module 3 and Product information accordingly.

Packaging materials for the capsule products (white PVC/PE/PVdC/PE/PVC foil and Alu foil) have been acceptably described and are considered adequate to provide suitable protection of the drug product. Bulk capsule packages are also sufficiently described.

Furthermore, a sample of the finished product in its intended package is requested to be submitted to facilitate the assessment of the container/closure system, for example its fitness for use.

3.1.3.4. Stability of the product

Registration stability studies according to ICH guidelines are ongoing and results from storage under long-term conditions and at accelerated conditions have been submitted. The bracketing strategy applied for the primary stability study design is considered acceptable.

A photostability study in accordance with ICH Q1B was performed.

The data submitted indicates adequate drug product stability. However, due to questions regarding the control of the drug product, no shelf life is accepted at this stage.

Bulk drug product hold time is considered acceptable for bulk capsules at general warehouse storage conditions of approximately 19 – 25°C (66°F to 77°F) and 30% to 60% relative humidity. Additional data from the ongoing confirmatory bulk stability study are requested. Accumulated stability studies also have to be performed.

3.1.3.5. Post approval change management protocol(s)

Not applicable.

3.1.3.6. Adventitious agents

Adequate information with respect to TSE issues is included in the excipients´ section of the Quality assessment report.

3.1.3.7. GMO

Not applicable.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The drug substance bardoxolone methyl is a non-hygroscopic white to off-white powder that shows good solubility in many organic solvents but is practically insoluble in aqueous solvents across the physiological range.

Some degradation of bardoxolone methyl has been observed during oxidative and photolytic stress conditions, but under long-term and accelerated conditions in accordance with ICH the active substance is very stable.

A final decision regarding the acceptability of the description of the GMP-process and the in-process controls applied will not be taken until the choice of starting material has been sufficiently justified (major objection).

The proposed starting material has been sufficiently characterized. The justifications for the specifications for EA01020 seem reasonable, but the specification is not considered fully acceptable until the choice of EA01020 as GMP-starting material has been fully justified.

The formation, control, and qualification of related substances are discussed in the impurities section of the dossier. An impurity formed under forced degradation conditions is also discussed.

The residual solvents potentially present in the drug substance are controlled in accordance with ICH Q3C, which is acceptable, and the information presented regarding elemental impurities is considered acceptable. Related substances are assessed for mutagenic potential according to ICH M7 and are classified as Class 4 or Class 5 compounds, and therefore treated as non-mutagenic impurities. Additional evaluation according to ICH M7 of all substances used in the active substance manufacturing

process is needed. The nitrosamine risk assessment confirms that risk of N-nitrosamine formation in the manufacturing process is very low due to the very low content of nitrosating agents available. In addition, hydroxylamine hydrochloride should also be assessed with regards to potential formation of nitrosamines.

The drug substance specification contains typical tests. The validation data presented for these analytical methods are acceptable in most parts, but additional data need to be presented for some methods.

The information presented regarding the drug substance batches produced and the batch analysis data presented for these batches are considered acceptable.

The justifications for the drug substance specifications are acceptable except regarding the justification of certain limits for which additional information is requested. In addition, inclusion of optical rotation testing in the drug substance specification is requested.

Information on the used reference standards is missing and should be presented.

Adequate data on the container closure system is presented.

Based on the presented stability results, the proposed re-test period without any special storage conditions can be accepted.

The drug product is presented as hard capsules in the two strengths 5 mg and 15 mg packed in blister packages.

The development of the drug product is well described but additional information needs to be submitted.

The drug product manufacturing process and process controls have been acceptably described. However, the proposed Proven Acceptable Ranges/Design spaces are not considered acceptably justified.

Adequate specification parameters have been included in the drug product specifications, but not all acceptance criteria are found acceptable. The nitrosamines risk evaluation is not yet considered acceptable and additional information/data is required. Hence, a Major objection is raised.

Awaiting the resolution of issues with respect to the control of the drug product, no shelf life is currently accepted.

3.2. Non-clinical aspects

3.2.1. Introduction

Bardoxolone methyl (BM), also known as RTA 402, is an orally bioavailable reversible inhibitor of Keap1 (Kelch-like ECH-associated protein 1). Keap1 acts as a negative regulator of Nrf2 (nuclear factor-erythroid 2-related factor 2) that is a transcription factor that modulates the expression of genes involved in inflammation, oxidative stress, and cellular energy metabolism. Based on a wide literature, the Keap1-Nrf2 pathway is described to play a key role in modulating the antioxidant response, coordinating metabolic reprogramming and being a driver in the resolution phase of inflammation by regulating the expression of genes involved in redox balance, mitochondrial metabolism, and inflammatory cytokine production. The Keap1-Nrf2 pathway appears as a central sensor of oxidative stress that rapidly responds to restore cellular homeostasis by regulating the expression of genes.

Alport syndrome is caused by mutations in genes encoding for Type IV collagen, which e.g., is a major constituent of the glomerular basement membrane (GBM) in the kidney. The mutated Type IV collagen

leads to an impaired basement membrane structure in the glomeruli that result in a disturbed glomerular filtration and CKD. In addition to the kidney involvement, the mutated Type IV collagen may also lead to bilateral sensorineural hearing loss and eye abnormalities in Alport syndrome. The severity of disease manifestations may differ by the inheritance pattern and the nature of the causative mutation. The most common inheritance pattern is X linked Alport syndrome (XLAS). Approximately 50% of males with XLAS develop kidney failure by age 25, increasing to 90% by age 40, but all forms of Alport syndrome are characterized by progressive nephropathy and therefore associated with an increased risk for progression to end-stage kidney disease (ESKD) at younger age.

3.2.2. Pharmacology

Mechanism of action

The relevance of targeting the Keap1-Nrf2 pathway for chronic kidney diseases is supported by genetic research data in humans demonstrating that the Keap1-Nrf2 pathway is suppressed in many forms of CKD, including Alport syndrome, and that this suppression correlates with impaired glomerular filtration rate (GFR) (Martini, 2014). The relevance of Nrf2 as a therapeutic target for kidney diseases is also supported by the phenotype of transgenic animals that are missing Nrf2 (Nrf2-knockout) or have constitutive activation of Nrf2 (through genetic knockdown of Keap1). The applicant propose that treatment with bardoxolone methyl targets the underlying pathophysiology of kidney disease by inhibiting acute and chronic inflammation-mediated and pro-fibrotic pathways.

BM activates the Keap1-Nrf2 pathway by binding to the cysteine residue 151 (Cys151) binding pocket on Keap1, as confirmed by X-ray crystallography (Cleasby, 2014; Huerta, 2016). Keap1 is a sensor protein that normally targets Nrf2 for degradation by the ubiquitin proteasome system. Binding to Cys151 causes a conformational change in Keap1 that prevents degradation of Nrf2 and leads to translocation to the nucleus. In the nucleus, Nrf2 binds to highly specific promoter regions of DNA called antioxidant response elements (AREs), which subsequently leads to transcriptional induction of hundreds of target genes.

3.2.2.1. Primary pharmacodynamic studies

Primary pharmacodynamics in vitro

The applicant present a basket of *in vitro* studies to characterize the pharmacodynamic effects of BM, spanning from Nrf target gene expression, restoration of mitochondrial dysfunction and reduction of proinflammatory signaling. No IC50 value for BM binding to its target, Keap1, is provided. The IC50 values presented is based on an *in vitro* assay for IFNγ-induced nitric oxide production in RAW 264.7 macrophages, which was used for a study where the pharmacological activity of BM was compared to BM metabolites. IC50 values of BM were determined separately alongside each metabolite which resulted in a range of 1.9-7.9 nM.

The effect of BM on Nrf2 target gene expression was investigated in cultured human kidney cells. Human podocytes, glomerular endothelial and mesangial cells were incubated with BM at concentrations of 0, 10, 50, 100, or 250 nM for approximately 16 hours, before the mRNA expression levels of Nrf2 target genes were quantified. BM dose-dependently increased the expression of the Nrf2 target genes HMOX1 (or HO-1), NQO1, and TXNRD1 in the human renal cell lines that were evaluated. In addition, Nrf2 activation by BM in renal cells *in vitro.*

have been demonstrated in many other studies conducted by the sponsor (e.g., Study RTA400-R-1801) and independent academic laboratories.

The effect of BM, (at 0, 3.1, 6.3, 12.5, 25 nM) on parameters of mitochondrial function was evaluated in IFNγ-stimulated murine macrophages (RAW 264.7). Oxygen consumption rate (OCR) was measured before the addition of mitochondrial inhibitors and after each sequential addition of 1 µM oligomycin, 1 µM FCCP, and 0.5 µM antimycin A and rotenone. Pre-treatment with BM at concentrations ≥6.3 nM significantly attenuated IFNγ-induced mitochondrial dysfunction, restoring the mitochondrial parameters toward vehicle control levels. Decreased mitochondrial function was manifested as lower levels of basal respiration, of ATP-linked respiration, and of spare respiratory capacity (i.e., the cells ability to respond to stress).

The effect of BM on inflammatory signalling in the form of IFNγ-induced nitric oxide (NO) production was evaluated in murine macrophages (RAW 264.7) that were pre-treated with vehicle (DMSO) or BM (0.8, 1.6, 3.1, 6.3, 12.5, 25, 50, 100, or 200 nM) for 2 hours and stimulated with IFNγ for 24 hours. BM dose-dependently decreased IFNγ-induced NO levels and decreased the levels of iNOS enzyme, responsible for NO production. The BM-induced reduction of iNOS protein expression was demonstrated to be Nrf2 dependent by utilizing a small interfering RNA (siRNA) knockdown of Nrf2. Similar results were observed for the BM analogue RTA 405 (results not shown by the applicant).

The effect of BM on inflammatory signalling was also evaluated as the effect on TNFα-induced mRNA expression levels of the proinflammatory MCP-1 and RANTES. Human mesangial cells were pre-treated with vehicle (DMSO) or BM (50 or 100 nM), followed by stimulation with TNFα. The mRNA expression levels of the TNFα-inducible targets MCP-1 and RANTES were determined. BM suppressed the TNFα-induced mRNA expression levels of both MCP-1 and RANTES in a dose-dependent manner. The applicant puts forward, that TNFα has been shown in the literature to contribute to the pathogenesis of progressive glomerulosclerosis in an *in vivo* model of Alport syndrome and blockade of TNFα provides beneficial effects on renal function (Ryu, 2012). Furthermore, the applicant provided a list of seven additional studies (mainly conducted in-house) investigating effects of BM on suppression of inflammatory activity in cultured renal and immune cells, supporting a possible anti-inflammatory MoA by BM.

For the comparison of the pharmacological activity of bardoxolone methyl and BM metabolites, the primary *in vitro* assay IFNγ-Induced nitric oxide production in murine macrophages (RAW 264.7) was used. BM was >800 times more potent than the metabolites M3, M4, M19, and M23 in suppressing IFNγ-induced NO production in RAW 264.7 macrophages, indicating that the BM metabolites possess minimal pharmacologic activity relative to parent. The major circulating metabolite, M30, is an endogenous molecule (thiocyanate), and its levels are not changed following BM administration. Consequently, no additional characterization of M30 was performed. The relevance of the IFNγ-induced nitric oxide assay system, as the applicant argues, is supported by the observation that in the mammalian inflammatory response, IFNγ plays a key role in stimulating the production of NO in macrophages (Bogdan, 2001). Moreover, NO is an important marker of pro-inflammatory macrophages and, together with secreted pro-inflammatory cytokines and ROS, contributes to the pathogenesis of many inflammatory diseases (Tang, 2019). Furthermore, the ability of BM and related analogues to suppress NO is abrogated in cells that are deficient in Nrf2, demonstrating that Nrf2 activation is required for NO suppression (Dinkova-Kostova, 2005). This reasoning can be followed.

Primary pharmacodynamics in vivo

The ability of BM treatment to trigger Nrf2 target gene expression in kidneys was investigated in female cynomolgus monkeys that received a 28-day BM treatment of 30 mg/kg QD or male and female cynomolgus monkey receiving a 12-months treatment of 5, 30 or 300 mg/kg QD. Samples were collected for clinical & urine chemistry, histology, mRNA quantification, glutathione quantification and enzyme activity assays. BM treatment (30 mg/kg) for 28 days resulted in: increased renal mRNA

expression of prototypical Nrf2 target genes (NQO1, SRXN1, TXNRD1, GCLC, and GSR); Increased renal protein expression of NQO1, primarily localized to tubules and increases in corresponding enzyme activity; Increased renal concentration of endogenous antioxidant Glutathione (GSH); Decreases in serum creatinine and blood urea nitrogen (BUN), and increased creatinine clearance. No histological evidence of structural damage to the kidney was observed after 12 months of daily administration (confirmed in the repeat-dose toxicology study). Overall, these data demonstrate that BM induces pharmacologic activation of Nrf2 in the kidneys after oral dosing in nonhuman primates and these effects are associated with improved kidney function. Furthermore, no to minimal histological evidence of structural damage to the kidney was observed after 12 months of daily administration.

To demonstrate Nrf activation in response to BM treatment, induction of the antioxidative enzyme Nqo1 in mouse kidney was studied. Nqo1 is suggested to be activated downstream to Nrf2. Since higher doses of or extended treatment with BM is toxic to small rodents, a single low dose (3 mg/kg) of BM treatment was used. 24 hours later renal Nqo1 protein and mRNA expression levels were determined. The BM treatment increased the mRNA and protein levels of Nqo1 in the renal cortex of wild-type but not Nrf2-null (Nrf2-/-) mice. The absence of response in the in the Nrf2-null mice indicates that the Nqo1 response is Nrf2 dependent. In the same study, a transcriptomic analysis of kidney tissue indicated that BM regulates the expression of genes involved in renal homeostatic processes, including Nrf2-mediated oxidative stress response, glutathione-mediated detoxification, and pentose phosphate pathway signalling. In addition, several literature references were provided by the applicant with supportive evidence that bardoxolone methyl and analogues increase the expression of Nrf2 target genes in kidney tissue.

According to the applicant, toxic metabolites are formed in rodent species and therefore very limited investigations have been carried out with BM in rodent models, restricted to low dose and short treatment duration. Due to these species-specific metabolites, suggested to cause toxicity in rodents, though not clearly shown not to be caused by BM itself, structural analogues to BM have been used as surrogates to investigate the pharmacology of Nrf2 activation in kidney disease models. The used structural analogues lack the methyl ester moiety at the C17 position and therefore do not form toxic C17-carboxylic metabolites. This strategy is based on that the structural analogues and BM share the pharmacophore and pharmacological activity.

The applicant present a high-level list of eight studies along with general findings demonstrating that analogues (and in some case BM) are active in multiple kidney disease models. For the three studies summarized below, more details were presented.

In the ICGN mouse model of nephrotic syndrome, the analogue RTA dh404 was administered by oral gavage at 10 mg/kg/day QD, from three to six weeks of age. The RTA dh404 treatment resulted in suppressed inflammation associated with decreased kidney fibrosis (SCr), Blood Urea Nitrogen (BUN), and urinary KIM-1 and NGAL; Increased number and improved ultrastructure of mitochondria; Increased number of cytochrome c oxidase (COX, complex IV) and succinate dehydrogenase (SDH, complex II) positive cells.

In the 5/6 nephrectomy model of hyperfiltration-induced chronic renal failure in rat, RTA dh404 (at 2 mg/kg) was administered once daily for 12 weeks. A decreased pressure-mediated glomerulosclerosis, tubulo-interstitial injury, inflammatory cell infiltration, and fibrosis was observed, along with decreased markers of oxidative/nitrosative stress and inflammation, in addition to decreased angiotensin receptor expression in the vasculature. An increased renal Nrf2 activation and decreased pro-inflammatory NF-κB (p65), p-IκB, and pro-fibrotic TGF-β levels was also seen. RTA dh404 appeared to be well-tolerated with no apparent adverse (clinical or macroscopic) effects observed (data not shown by the applicant).

In a Protein-induced nephropathy model in uni-nephrectomized mice receiving daily protein injections for 28 days, causing protein overload-induced interstitial inflammation and fibrosis, RTA 405 was

administered as 100 mg/kg in chow for 23 days. This treatment, with no exposure values presented, resulted in decreased levels of interstitial inflammation, as assessed by accumulation of monocytes and macrophages, and decreased fibrosis, indicated by significantly reduced peritubular smooth muscle actin staining.

These studies with structural analogues indicate that the BM analogues may target various structural processes that contribute to irreversible kidney function loss. The suggested MoAs could be valid also for BM, provided BM shares the same pharmacophore and pharmacological activity with the structural analogues.

BM treatment cause an increased eGFR in clinical studies. An increased eGFR could be caused by an increased blood pressure or pressure over the glomeruli that subsequently could lead to glomeruli damage. However, the applicant claims the observed increased GFR can be explained by BM acting by "Novel mechanisms" not dependent on increased pressure over the glomeruli. Their view is supported by a set of studies described below with BM or structural analogues indicating that the increase in GFR may be explained by such "Novel mechanisms" i.e., BM may act by an effect on glomerular surface area; or by an effect on Angiotensin II-induced mesangial cell contraction causing glomeruli volume changes; or by a reduction of endothelial dysfunction; and not by increasing systemic or intra-glomerular blood pressure.

In vivo multiphoton microscope (MPM) imaging was used to evaluate the diameter of the afferent/efferent arterioles, single-nephron GFR (SNGFR) by monitoring of freely filtered lucifer yellow, and glomerular permeability by monitoring of FITC-conjugated bovine serum albumin. Nrf2-knockout (Nrf2-KO), Nrf2-activated Keap1-knock-down (Keap1-KD) or C57BL/6 (Control) mice were administered with the BM analogue RTA dh404, 10 mg/kg/day by oral gavage for 1w. The treatment resulted in increased single-nephron GFR (SNGFR), and as the applicant claims, with concomitant increasing glomerular volume without changes in blood pressure. However, in Figure 14, *Pharmacology Written Summary*, a significant difference in glomerular volume is only indicated between Keap1-KD vs. WT but not for WT+RTA404 vs WT and the statement on blood pressure is not supported by any shown data. Thus, effects of increased SNGFR were also observed in Keap1-knockdown mice, which have constitutive genetic activation of Nrf2. SNGFR was significantly higher in Keap1-KD mice than in the control group (9.13±0.55 vs 4.40±0.39 nl/min, $p<0.05$). In addition, RTA dh404 administration increased the SNGFR in control mice but not in Nrf2-KO mice (6.00±0.40 vs 4.66±0.35 nl/min, $p<0.05$). These observations indicate a Keap1/Nrf2 dependent mechanism. For the glomerular afferent/efferent arteriole ratio no significant alterations were observed. Furthermore, the RTA dh404 treatment did not affect the glomerular permeability of albumin and 40 kDa dextran. In conclusion, the increase in GFR appeared not associated with changes in glomerular permeability of albumin or with changes in afferent/efferent arteriolar ratios, providing support for a MoA not associated with increased intraglomerular pressure. These changes were not observed when the BM analogue was administered to Nrf2-null mice, indicating the critical importance of Nrf2 for the increases in SNGFR. It is noted, the provided reference, Kidokoro, 2019a, is a meeting abstract offering limited possibilities for assessment. Also, it appears to not show any systemic blood pressure measurement values. Moreover, in contrast to what is referred to as source in Figure 14, for results from RTA dh404 treatment, Kidokoro 2019b does not describe data from studies with RTA dh404 treatments but other non-bardoxolone related agents.

The contractile state of mesangial cells in the glomeruli affect the glomeruli volume and thereby the available glomerular surface area for filtration which also affect the GFR such as less contracted mesangial cells will lead to increased glomeruli volume and surface area which in turn lead to an increased GFR. The BM and BM analogue effect on angiotensin II-induced mesangial cell contraction and glomeruli volume changes was investigated ex vivo. Human mesangial cells were untreated (UT) or pre-treated with DMSO; vehicle) or BM (BARD) for 16h and then treated with 1 µmol/L of

angiotensin II (Ang II) for 30 minutes. The planar surface areas were calculated using ImageJ software. In addition, rats were treated with RTA 405 at 100 mg/kg/day or sesame oil vehicle by oral gavage for 3 consecutive days. Glomeruli were freshly isolated and exposed for angiotensin II (1 µmol/L). Glomerular volume was estimated from the spherical surface area that were calculated using ImageJ software. The ex vivo angiotensin II induced decreased human mesangial cell contraction was significantly inhibited in a concentration- and time-dependent manner by ex vivo BM exposure. Furthermore, glomeruli from rats treated with BM analogue RTA 405 were resistant to angiotensin II-induced contraction ex vivo. These results provide evidence that BM and related analogues can increase the glomerular surface area for filtration in the presence of angiotensin II.

To assess whether the increases in whole glomerular surface area translate to increased GFR, inulin clearance was quantified in rats after angiotensin II infusion and treatment with RTA 405 at 100 mg/kg /day by oral gavage QD for 3 consecutive days. Blood pressure measurement in conscious rats was conducted at baseline and 8 h post dose on day 3 via tail cuff. Blood pressure response to acute infusion of Ang II was measured in anesthetized rats (pentobarbital IP, 50mg/kg). The left carotid artery was cannulated for blood pressure recording and analysis. Rats treated with RTA 405 showed a reversal of the angiotensin II-induced reduction of inulin clearance, resulting in increased GFR as compared to untreated. The GFR values were similar to the rates in control rats that did not receive angiotensin II, thus indicating RTA404 prevented the angiotensin II induced contraction of mesangial cells and glomeruli which normally would have led to a decreased GFR. RTA 405 treatment also increased the basal GFR levels relative to treatment with vehicle alone. Thus, RTA 405 increased the renal filtration fraction (the ratio of GFR to renal plasma flow) but did not affect blood pressure or renal plasma flow. This demonstrates that the RTA 405 BM analogue can reverse angiotensin II-mediated impairment of the glomerular surface area (Kf), which may also apply to BM and, if so, this mechanism may contribute to the observed BM-induced GFR increase in the clinical trials.

It was also investigated whether the BM structural analogue RTA dh404 could restore the vasodilatory response to acetylcholine in the rat 5/6 nephrectomy model of hyperfiltration-induced chronic renal failure (here denoted as CKD). The impaired vasodilatory response to acetylcholine in this model was used as a read out for endothelial cell dysfunction. The acetylcholine-induced vasorelaxation was markedly impaired in the untreated CKD group. RTA dh404 decreased this endothelial cell dysfunction through restoration of the vasodilatory response to acetylcholine. The CKD also significantly lowered the Nrf2 content in the nucleus, as well as Ho-1 and Sod2 protein expression, whereas Keap1 protein expression was significantly increased. RTA dh404 administration fully or partially restored the Nrf2 content in the nucleus, as well as Sod2, Ho-1, and Keap1 protein expression. In another experiment, reactive oxygen species (ROS) and NO was measured in human umbilical vein cells (HUVECs). The background to this study, according to the applicant, is that inflammation-associated ROS induce endothelial nitric oxide synthase uncoupling and the resultant loss of endothelial function can reduce GFR. Moreover, endothelial dysfunction is characterized by reduced bioavailability of NO and decreased vasodilation. In the study confluent HUVECs cells were treated with BM at 0, 30, 100, 300 nM. After 48h mitochondrial superoxide (ROS) and NO levels were measured. BM decreased ROS and increased endothelial NO in a dose-dependent manner. The suppression of ROS and induction of endothelial NO was attenuated when Nrf2 levels were decreased with siRNA, indicating that the effects were mediated through Nrf2. In summary, the presented results show possible MoAs for how BM may reduce endothelial dysfunction in CKD.

3.2.2.2. Secondary pharmacodynamic studies

BM was evaluated (at 1 µM and 10 µM) for potential *in vitro* binding in a panel of 37 off-target receptors, ion channels and transporters, and for potential inhibitory activity on 6 enzymes. At a concentration of 10 µM, BM significantly (>50%) inhibited reference compound binding to the D1

dopamine receptor (55.7%) and the CB1 cannabinoid receptor (58.8%). At 1 µM, BM did not significantly inhibit reference compound receptor binding or enzyme activity. The *in vitro* concentration of 1 µM BM corresponds to approximately 500 times the mean maximum steady-state unbound drug plasma concentration (Cmax) in Alport syndrome patients administered a 30-mg oral dose.

Because of the wide spectrum of effects inhibition of KEAP1 and the subsequent activation of Nrf2 may have, involving increased transcription of numerous genes that collectively is involved in the regulation of the redox balance, mitochondrial function and inflammation, bardoxolone treatment can be expected to induce a wide set of pharmacological effects affecting multiple physiological processes. In the context of secondary pharmacodynamics, the applicant discuss a number of such Nrf2/KEAP1 associated physiological (and pathological) processes that are affected by BM treatment and associated with the present CKD indication. A vast literature in conjunction with some Reata Pharmaceuticals associated studies are presented by the applicant as *"Additional Pharmacological Characterization"* related to findings in nonclinical toxicity and clinical studies, of which a brief description will follow below (these findings are Furter discussed in the nonclinical toxicology and clinical section, respectively).

Increased liver weights and biliary hyperplasia have been observed in the pivotal nonrodent species (ie, monkeys and minipigs) GLP toxicity studies following repeat oral administration of bardoxolone methyl. Therefore, a study was conducted in rats with RTA dh404 to investigate the pharmacological basis for these observed effects of bardoxolone methyl on the liver. Treatment with the BM analogue RTA dh404 (3, 10, or 30 mg/kg, QD for 7 days) dose-dependently increased bile flow and biliary excretion of GSH, without any alterations in bile acid profiles, consistent with pharmacologic activation of Nrf2. Keap1-knockdown mice, which have constitutive activation of Nrf2, also have increased bile flow and increased hepatobiliary concentrations of GSH (Reisman 2009).

Adult patients with Alport syndrome who received BM, experienced reductions in body weight that were more pronounced in patients who were overweight at baseline (see clinical section). For this reason, the applicant refers to that effects of Nrf2 on various body weight associated metabolic pathways such as lipid synthesis, fatty acid oxidation, glucose metabolism, and mitochondrial energy production are well documented (Nrf2 Activator Pharmacology Summary Report, 2020). Moreover, that there is a wide literature showing in particular that both genetic and pharmacologic activation of Nrf2 have beneficial effect on glucose utilization e.g. by decreasing plasma glucose and increasing glucose tolerance; suppressing the synthesis of new fatty acids, promoting the oxidation of existing fatty acids and reducing lipid accumulation in adipose tissue.

BM treated Alport patients showed increases (mild to moderate) in serum levels of brain natriuretic peptide (BNP) and N-terminal pro-peptide equivalent -BNP (NT-proBNP), (as noted in SmPC 4.8). In the literature several studies have demonstrated that weight loss induced by dietary intervention, bariatric surgery, and/or exercise programs correlates with a small, but significant, increase in circulating BNP levels, indicating that BNP levels can be positively influenced by changes in body weight and associated metabolic parameters. Based on these observations, the applicant hypothesized that the small increase in BNP observed following treatment with BM in the clinic could be a marker of metabolic reprogramming associated with increased fatty acid oxidation and energy expenditure. To test this hypothesis, a study was conducted in mice fed a high-fat diet for 12 weeks to assess the effects of 2 different BM analogues (QD, oral gavage for 12 weeks) on body weight, Nrf2 activation, and BNP expression (Study RTA-P-19008). Treatment with RTA 403 (15 mg/kg/day) completely attenuated weight gain in this model, while the less potent Nrf2 activator, RTA 405 (25 or 50 mg/kg/day), lowered but did not completely prevent the high-fat diet-induced weight gain. RTA 403 also significantly increased expression of the Nrf2 target gene Nqo1 in the heart, whereas RTA 405 had a more modest effect. In addition, cardiac Nqo1 mRNA expression, a measure of Nrf2 activity, and the

observed prevention of weight gain correlated with significantly higher levels of BNP (Nppb) expression in the heart.

In patients with Alport syndrome, BM was associated with mild to moderate, reversible elevations in serum aminotransferase activity, specifically alanine aminotransferase (ALT) and aspartate aminotransferase (AST), (as noted in SmPC 4.8). The applicant put forward that ALT and AST have important and complex physiological roles, and that these enzymes are not simply biomarkers of hepatic injury. Several studies were carried out to illustrate the association of Nrf activation to changes in transaminase levels and that BM can regulate aminotransferase gene expression also in extrahepatic tissues. In mice, genetic activation of Nrf2 (Keap1-knockdown) increases hepatic and renal ALT mRNA levels, whereas genetic deletion of Nrf2 (Nrf2-null) decreases them, with correlative serum levels of ALT (Study RTA402-P-1023). Exposure of cultured cells derived from liver, colon, skeletal muscle, macrophages, and proximal tubule to BM for 16-18 hours (at 10 – 1000 nM in various intervals for various cell types) results in concentration-dependent increases in both ALT and AST mRNA levels (Study RTA400-R-0802; Study RTA400-R-1012). Moreover, treatment of mice with two BM analogues Omaveloxolone and TX63682 with similar oral bioavailability (at 1, 3, or 10 mg/kg/day from 6 to 9 weeks of age) in a model of non-alcoholic steatohepatitis (NASH) resulted in an increase in serum transaminases, despite significant improvements in overall liver health and energy homeostasis (Reisman, 2020). A different aspect is that two isoforms of ALT and AST have been identified, each encoded by a discrete gene. ALT1 and AST1 are cytosolic proteins, whereas ALT2 and AST2 are localized to the mitochondria. The tissue distribution of these isoforms was investigated (RTA400-R-1004). Although ALT1 protein levels were highest in liver, this protein was also strongly expressed in adipose, kidney, heart, and skeletal muscle, and detectable in colon, pancreas, lung, and breast tissue. ALT2 protein levels were generally lower than ALT1 protein levels in the tissues examined but were abundant in liver, adipose, skeletal muscle, and brain. AST1 protein levels were highest in liver, heart, skeletal muscle, and brain, whereas AST2 protein levels were highest in liver, kidney, heart, skeletal muscle, brain, small intestine, and lung. Aminotransferase activity detected in the serum is presumed to be due to the release or leakage of aminotransferase enzymes from their tissues of origin; however, the exact mechanism of the release is not understood. Moreover, there is evidence to suggest that release of ALT and AST from cells can occur in the absence of any cellular toxicity *in vitro* (Josekutty, 2013). The current biochemical assays used to measure serum ALT and AST activity are incapable of determining from which tissue(s) the enzymes were released adding uncertainty to the origin of the elevated serum aminotransferase activity.

A transient increase in albuminuria (assessed as urine albumin-to-creatinine ratio (UACR)) have been observed in clinical trials with BM. Albuminuria is used as a measure of kidney function and an increase can be an indication of reduced glomerular integrity and endothelial dysfunction. A chronically increased intraglomerular pressure is harmful to the filtration barrier and could be driving such a kidney damage. However, the applicant presents a number of findings to demonstrate that the BM treatment induced increase in albuminuria is a reversible pharmacological effect related to increases in eGFR and reduced protein reabsorption in the proximal tubules, and not the result of irreversible kidney damage. An observation pointing in this direction is that the BM analogue treatment did not increase glomerular permeability to albumin as measured in the *in vivo* multiphoton microscopy study of SNGFR in mice described above (Kidokoro, 2019a). Furthermore, studies in cynomolgus monkeys demonstrate that BM (30 mg/kg/day) orally once daily for 28 days downregulates expression of the megalin protein, a component of the megalin-cubilin complex, which is involved in protein reabsorption in the proximal tubules. The downregulation of megalin occurred in conjunction with increased Nrf2 target gene expression and suppression of endothelin-1 signalling. (Study RTA402-P-1117; Reisman, 2012).

In addition, *in vitro* and *in vivo* studies were conducted to evaluate the effects of BM (and/or analogues) on the endothelin signalling pathway in search for an explanation of the BM associated findings of congestive heart failure (CHF) secondary to fluid overload in Type 2 diabetic patients with Stage 4 CKD. However, although extensively described, the beneficial effect is not entirely clear to the assessor, as a reduced ET1 signalling appears both causing the fluid overload with subsequent congestive heart failure and being suggested as a beneficial effect behind BM treatment. Furthermore, the studies and reasoning are not reflected in the applicant's Nonclinical overview.

3.2.2.3. Safety pharmacology programme

An in-vitro hERG test in HEK293 cells gave a potassium channel inhibition estimate of ~9.5% at 0.15uM bardoxolone methyl (see discussion). The in-vivo safety pharmacology assessment was conducted on dog (CNS) and cynomolgus (cardiovascular, pulmonary). An FOB-test in dog at 5-80mg/kg (single oral gavage, sesame oil vehicle) did not generate any abnormal or adverse behaviour (clinical signs or FOB tested behaviours). In a cynomolgus study (5, 60 and 120mg/kg single oral gavage using sesame oil as vehicle, use of the same animals but with one 1w washout intervals), there was a mostly transient (within 20h post-dose) change in systolic, diastolic, and mean arterial pressures (moderate reduction), heart rate (moderate reduction) and ECG parameters (weak to moderate increase in RR and PR-intervals, increase in QT-intervals, and decrease in cQT-intervals) at ≥5mg/kg. With regard to pulmonary endpoints, there was a slight trend of reduced mean respiratory trend at all doses in males and females (most cleat at 120mg/kg) and a clear reduction in mean tidal volume (at most a difference of control ~50mL to high dose ~30mL) and mean minute volume (at most a difference of control ~1750mL/min to high dose ~1000mL/min) in males at 120mg/kg. It can also be noted that oral exposure led to emesis in 5 and 120mg/kg doses (more than occurred in controls). Overall, this gives a NOAEL of <5mg/kg (see also discussion).

No toxicokinetic data was available for the cynomolgus safety pharmacology study with its effects at ≥5mg/kg, but in a cynomolgus PK-study that used a ~6mg/kg oral dose with the most representative formulation (Eudragit SDD 7.5% HPMC), the C_{max} was 17.4ng/mL, and the $AUC_{0\text{-}72h}$ was 251ngxh/mL. Based on a clinical AUC of 223ngxh/mL and C_{max} of 17.2ng/mL, this gives a rough low-dose margin of 1.13x (AUC) and 1x (C_{max}). If plasma protein binding is included (94.4% for human, 97.4% for cynomolgus), one gets unbound values corresponding to 0.52x (AUC) and 0.47x (C_{max}). In another cynomolgus PK-study using a ~10mg/kg dose with micronized crystalline formulation (likely the closest to the crystalline/sesame oil formulation used in the safety pharmacology study), the $AUC_{0\text{-}72h}$ was 134ngxh/mL and the C_{max} was 5.52ng/mL. This gives a total concentration margin of 0.6x (AUC) and 0.32x (C_{max}) and an unbound margin of 0.28x (AUC) and 0.15x (C_{max}). Overall, this indicates that there are no safety margins to human (≤ 1x) for the cardiovascular findings.

3.2.3. Pharmacokinetics

Formulation

The drug formulation development for bardoxolone methyl has shifted from an initial crystalline form of the drug substance, to an amorphous form and finally a spray-dried dispersion (SDD) form. The formulation intended for commercial use comprises of capsules containing a spray-dried dispersion containing 40% bardoxolone methyl and 60% polymer (Eudragit® L100-55).

Absorption

Bardoxolone methyl displays low permeability in MDCKII-cell monolayers in-vitro (at 1uM and 5uM) based on an apical to basal direction permeability estimate of 0.7×10^{-6} and 0.8×10^{-6} cm/sec. It is

not a substrate for P-gp or BCRP. In cynomolgus, the oral exposure bioavailability at an oral dose of ~10mg/kg was between 2.8% and 24.8% depending on the formulation (crystalline or amorphous/SDD) with Eudragit formulations providing the highest uptakes. The formulation understood to be not identical but the most representative of the late-stage clinical trial and commercial formulation is Eudragit SDD 7.5% HPMC. At doses of ~2mg/kg and ~6mg/kg respectively, the bioavailability for this formulation is 19.1% and 13.6%. Bioavailability has not been assessed for any other animal models.

In oral exposure single-dose PK studies, only one mouse and one rat study used more than one dose strength. For mouse, between doses 10 and 100mg/kg, the $AUC_{0\text{-}16h}$ values (349 and 1740ngxh/mL respectively) were less than dose-proportional (internal dose difference ~5x compared to external dose difference of 10x). For rat, between doses 0.5 and 4.5mg/kg, the $AUC_{0\text{-}16h}$ values (77.3 and 829.6ngxh/mL respectively) were slightly greater than dose-proportional (internal ~10.7x compared to external 9x). Among repeat-dose PK studies, there were only one minipig and one dog study with more than one dose strength. In Göttingen minipig, between minimum ~3.6mg/kg and maximum ~15.1mg/kg (28d exposure), the $AUC_{0\text{-}72h}$ values were roughly dose proportional between ~3.6mg/kg (100ngxh/mL) and ~7.2 mg/kg (246ngxh/mL; internal 2.5x compared to external 2.0x) and less than dose-proportional between ~7.2mg/kg and ~15.1 mg/kg (283ngxh/mL; internal difference 1.2x compared to external difference of 2.1x). For dog, between minimum ~2.5mg/kg and maximum ~25mg/kg (14d exposure), the $AUC_{0\text{-}72h}$ values were roughly dose proportional between ~2.5mg/kg (86ngxh/mL) and 12.5mg/kg (436ngxh/mL; internal difference 5.1x compared to external difference of 5.0x) and between 12.5mg/kg and 25mg/kg (686ngxh/mL; internal difference 1.6x compared to external difference of 2.0x).

The apparent volume of distribution (Vd) for mouse was between 174.9L/kg and 200.2L/kg (single oral gavage doses between 3 and 100mg/kg). For rat, the apparent Vd was between 28.4 and 62L/kg (for single oral gavage doses between 0.10 and 4.5mg/kg). For cynomolgus, the Vd was 44L/kg after a single intravenous injection of 0.22mg/kg. After oral gavage with different Eudragit SDD formulations (single dose of ~6mg/kg), the Vd was between 63 and 84L/kg (apparent Vd between 455 and 833L/kg). In a separate cynomolgus study, after single oral doses of ~2 and ~20mg/kg, the Vd was between 55-80L/kg (~2mg/kg, apparent Vd 347-418L/kg) and 51-58L/kg (~20mg/kg, apparent Vd 377-499L/kg) respectively. No Vd was calculated for minipig or dog.

Apparent clearance (CL) for bardoxolone methyl in mouse (single dose, oral gavage) was between a minimum of 24.8L/h/kg (from 10mg/kg dose) and a maximum of 56.8L/h/kg (from 100mg/kg dose). In rat, the apparent clearance was between 5.3 and 9L/h/kg (oral gavage doses between 0.5 and 4.5mg/kg). In cynomolgus, after a single intravenous injection of 0.22mg/kg, the clearance was 40L/h/kg. After different oral Eudragit SDD-formulations with a dose strength of ~6mg/kg, the clearance was 3.5-3.9L/h/kg (apparent clearance between 23.6 to 45.5L/h/kg). Oral Eudragit SDD formulations with a dose of ~2 and ~20mg/kg gave a clearance of 3.3-3.7L/h/kg (~2mg/kg; apparent clearance 19.3-20.8L/h/kg) and 2.8-2.9L/h/kg (~20mg/kg; apparent clearance 20.9-21.5L/h/kg) respectively. No CL was calculated for minipig or dog.

The termination half-life values ($t_{1/2}$) for rodents where 2.4h and 4.9h (mouse single dose, 10 and 100mg/kg) alternatively 3.1h and 4.3h (rat single dose, 0.5 and 4.5mg/kg). For minipig, the half-life increased from 10.7h (repeated low dose of ~3.6mg/kg) to 23.8h (repeated high dose of ~15.1mg/kg). For dog, the half-life ranged between a minimum of 10.2h (repeated dose of ~2.5mg/kg) and a maximum of 27.5h (repeated soe of ~12.5mg/kg).

For dog, there was no or weak dose accumulation after 14d oral exposure at ~2.5mg/kg but moderate at ~25mg/kg (1.68x-1.86x), indicating a dose-dependent increase in dose accumulation. In an 7d

repeat-dose cynomolgus PK-study (oral exposure, ~30mg/kg), there was also moderate dose accumulation (1.6x-1.8x).

Distribution

Bardoxolone methyl has a high degree of in-vitro plasma protein binding (94.4%-97.8%) across species, with human having the lowest binding at 94.4% followed by Beagle dog (96.7%), Sprague Dawley rat (97.2%), cynomolgus (97.4%), CByB6F1 mouse (97.6%) and Göttingen minipig (97.8%). It remains unclear what the plasma protein binding is for rabbit (used in a non-pivotal toxicological EFD study). For the max doses used in the different oral exposure PK-studies, this gives free and free unbound concentrations of 0.792uM and 0.019uM respectively for mouse (from C_{max} 400.3ng/mL at 100mg/kg), 0.34uM and 0.0095uM respectively for rat (from C_{max} 172ng/mL at 4.5mg/kg), 0.11uM and 0.0029uM respectively for cynomolgus (from C_{max} 57.3ng/mL at 30mg/kg), 0.067uM and 0.0015uM respectively for minipig (from C_{max} 34.1ng/mL at ~15.1mg/kg), and 0.11uM and 0.0035uM respectively for dog (from C_{max} 54ng/mL at ~25mg/kg). Metabolites M3 (1,2-DH-21β-OH-29-OH bardoxolone methyl) and M19 (1,2-OH-29-COOH-bardoxolone methyl) demonstrated an in-vitro human plasma protein binding of 98.5%. Bardoxolone methyl mean whole blood-to-plasma concentration ratios were 0.62x, 0.60x, and 0.60x for rats, monkeys, and humans, respectively.

In a Quantitative Whole-Body Autoradiography (QWBA) study in pigmented male rats (8mg/kg, single oral capsule exposure, sampling to 672h post-dose), the highest levels of ^{14}C-radiolabelled active substance radioactivity were found in the content of the gastrointestinal (GI) tract. Highest organ/tissue peak levels (>3400ng equivalents/g) were observed after around 4-8h with the highest levels found in: 1) liver, 2) kidney cortex, 3) kidney, 4) kidney medulla, 5) myocardium, 6) stomach mucosa, and 7) brown fat. The lowest peak levels were in eye and eye lens. The tissue:plasma concentration ratios were >1x for most measured samples 4 to 12h post-dose. There was some radioactivity in both central nervous system (CNS) tissues and testis – demonstrating passage through the barriers - but at low levels for both organ/tissue types. The tissue:plasma concentration ratio for central nervous system (CNS) tissues was <1x and peak levels were low (342-530ng equivalents/g for T_{max} at 4-8h across both rat strains). For testis, the tissue:plasma concentration ratio was 0.715x-1.32x (287-671ng equivalents/g for T_{max} 4-8h across rat strains). The radioactivity levels of pigmented rats (Long-Evans) were similar to those of non-pigmented rats (Sprague-Dawley). One additional organ/tissue found in non-pigmented rats was salivary glands. Overall, in pigmented rats, elimination was nearly complete for most tissues by 672h post-dose; only preputial gland had low concentrations of radioactivity. In non-pigmented rats, elimination was mostly complete by 168h. No females were investigated, so distribution to female reproductive organs has not been characterized. This is a weakness in the PK-dossier that is partially compensated by a study with LC-MS/MS-based distribution quantification of Bardoxolone methyl in cynomolgus (25mg/kg, amorphous formulation, sampling for up to 24h post-dose). While difficult to use for the purpose of exact quantification, the organs with highest uptake were the mammary (both in males and females) and ovary. In male cynomolgus, and in contrast to rats, there were high levels in prostate. The cynomolgus levels in kidney and liver were low despite having high levels in rat. As for rat, there was very little uptake in the cynomolgus CNS.

Metabolism

Bardoxolone methyl is extensively metabolised. In radiolabelled plasma samples from cynomolgus and human, the parent molecule corresponded to only ~0.27% and ~0.24% of the total radioactivity. In-vivo metabolism of bardoxolone methyl seems to primarily involve involved reduction and oxidation of the A- and E-ring moieties.

- Direct bardoxolone methyl metabolites

- 1,2-Epoxy RTA-402 [M28]
- 1,2-dihydro RTA-402 [M29]
- RTA-401 (carboxylic acid metabolite)
- SCN^- [M30]
- Putative hydroxylated metabolites

There are issues with the position of the radiolabel in bardoxolone methyl (at the C2-position on the A-ring; see Discussion). Among the identified/reported metabolites that retain the radio-label, the intermediary A-ring altered 1,2-dihydro RTA-402 (or M29) seems to be the basis for several downstream structurally characterized metabolites (and several unidentified metabolites; described as putative hydroxylated metabolites E_1, E_2, and E_3). Four 1,2-dihydro RTA-402 derived metabolites were identified in cynomolgus plasma samples: M3 (1,2-DH-21β-OH-29-OH bardoxolone methyl), M19 (1,2-OH-29-COOH-bardoxolone methyl), M23 (1,2-DH-30-COOH-bardoxolone methyl). Another direct descendent of the parent compound is an A-ring epoxide metabolite (1,2-Epoxy RTA-402 or M28). A third direct descendant metabolite is the M30 – a cleaved thiocyanate (SCN^-) group derived from the A-ring position where the applicant usually puts the radiolabel (^{14}C). The generation of the presently predominant M30 (e.g., biochemical process, enzymes) remains unclear. Besides the structurally identified metabolites, a number of chromatographically unresolved structural isomers were also detected (named A, C, D_1 and D_2 and described as putative hydroxylated metabolites of bardoxolone methyl). M30 has been found in both cynomolgus and human plasma (cynomolgus 96.8% of total radioactivity; human 76.3% of total radioactivity). Certain E-ring metabolites (carboxylic acid metabolites or 'C17-metabolites') were also detected but only in rodents (plasma), hamster (plasma) and minipig (in liver but not plasma). The metabolites were generated via ester hydrolysis at the C17 position, resulting in the metabolites RTA-401, 1,2-dihydro RTA-401, and 1,2-dihydro RTA-401-acyl glucuronide. The detection of these C17 metabolites were based on non-radio-labelled LC-MS/MS measurements. Regarding the putative hydroxylated metabolites (A, C, D1, D2, E1, E2, and E3), the main difference seems to be the absence of the A-metabolite in humans and cynomolgus. Minipig seems also to have fewer of the metabolites than the other animal models (only C, D2 and E3).

Artificial biotransformation using microsomes from different animal species generated additional metabolites (between 0.5uM to 10uM bardoxolone methyl depending on microsome source), including the two carboxylic acid metabolites RTA-401 and 1,2-Dihydro RTA-401 via demethylation of the $C0_2CH_3$ chemical group at position 17 in bardoxolone methyl (found or implied with mouse, rat, hamster, rabbit and minipig microsomes). The previously noted epoxide metabolite was also generated in all microsomes variants (i.e., human, mouse, rat, hamster, rabbit, dog, minipig and cynomolgus) and was also discovered in faeces samples from human (but not in human plasma). Metabolites 1,2-Dihydro RTA-401 and 1,2 Epoxy RTA-402 could also be generated non-enzymatically (mainly the former which showed increase over time, while the latter remained at < ~1.2% over incubation time). No primary hepatocyte studies have been conducted.

Analysis of a battery of human recombinant CYP450s indicate that CYP2C8, CYP2C9, CYP3A4 and CYP3A5 enzymes are the most potent CYPs for bardoxolone methyl biotransformation, but it remains unclear which CYPs, or other enzyme classes, are connected to the different metabolites. The generation of C-17 metabolites in rat is dependent on CYP2C6 (tested in supersomes at 100uM bardoxolone methyl), an enzyme that is not found in primates.

It can be noted that in all animal PK-studies, plasma (and milk) samples were fortified with sodium sulfite (0.25% w/v) to prevent ex-vivo bardoxolone methyl degradation.

Elimination

A mass balance study with cynomolgus and 168h post-dose sampling found that less than 90% (61.8%-86.6% depending on dose and exposure route) of the radioactivity was recovered in excreta and bile. As the radio-label position used in the mass balance study was in the metabolically unstable position (see above), the reported results are unlikely to represent the full elimination fate of all metabolites.

After oral exposure (oral gavage with sesame oil alternatively gelatine capsules), most of the measurable bardoxolone methyl and its metabolites remained in the cynomolgus gastrointestinal system and was secreted via faeces. Depending on formulation, total faeces levels were ~62-87%, whereof a maximum of only ~2.7% was detected in bile. There was little reduction of plasma levels in the up to 168h post-dose samples.

With intravenous exposure, the urine proportion was ~2% and the bile proportion was instead ~60%, making bile the main pathway of excretion in cynomolgus under parenteral conditions. Urine levels after oral exposure were <0.7%. It is unclear what the radioactivity corresponds to in the urine, but in a comparative cynomolgus and human metabolite study, only the M30 metabolite (SCN-) was discovered in human urine (it was not detected at all in human faeces) – indicating that the same may hold true for cynomolgus urine.

It can be noted that in the QWBA distribution study in rats, ^{14}C-bardoxolone methyl was not detected at all in the bile of pigmented and non-pigmented rats (measured up to 672h post-dose), indicating that biliary elimination is not relevant or only a very minor route in rats.

3.2.4. Toxicology

The toxicological profile of Bardoxolone methyl (RTA 402) has been evaluated in a full program of non-clinical studies and the pivotal studies were performed in accordance with GLP regulations. Repeated-dose toxicity studied included mice, rats, hamsters, dogs, monkeys and minipigs. The toxicity profile of RTA 402 was markedly different between different species with severe toxicity in rodents and dogs. Adverse toxicities have been identified as well as issues which should be further discussed by the applicant.

Repeated dose toxicity studies were conducted with two different forms of bardoxolone methyl drug substance: crystalline or amorphous. ≤28-day repeated dose studies were conducted with the crystalline form, whereas subsequent GLP toxicity studies were conducted with the amorphous form (improvements in oral bioavailability). The amorphous form of drug product was used throughout the majority of clinical development.

Noteworthy findings

Multiple toxicological findings were reported, and some findings recured in several species but with different severity while other findings showed a more species-specific pattern. Findings in the kidneys are of special concern given the proposed indication and patient population. Kidney findings were most severe in rodents while minipigs had less affected kidneys, occasional findings were reported from dogs and monkeys. The GI tract is also of particular concern given the AEs reported in the clinical trials and that GI-tract findings were reported from all species, see LoQ.

Relevance of animal models

Studies in rodents

Oral administration once daily of RTA 402 to mice, rats and hamsters caused significant toxicity and mortality at exposures of RTA 402 even lower than clinical exposure. The applicant claims that the

toxicity seen in rodents (mouse, rat and hamster) is caused by a rodent-specific metabolism of RTA 402 producing the C17-carboxylic metabolite RTA 401 and that rodents, therefore, are not useful models for predicting human toxicity. However, the mechanism of toxicity for RTA 401 has not been established and it is not clear if all or only some of the adverse changes observed in rodents were caused by RTA 401, or if some, in fact, were caused by RTA 402. No in-vivo studies with these metabolites have been submitted and hence, the cause of the toxicity in rodents have not been established. This metabolite profile causes challenges in interpretation of rodent data and the relevance of rodents requires further discussion.

Studies in dogs

Dogs that received repeated doses of bardoxolone methyl exhibited severe acute gastrointestinal (GI) toxicity. It was pointed out in previous scientific advice that an understanding of the underlying mechanism would be of value. The applicant has provided the following statement: "*The precise mechanism for the observed severe gastrointestinal toxicity in dogs is not completely understood; however, it may be related to an intrinsic sensitivity of dogs to anti-inflammatory agents, species-specific gut irritation from bardoxolone methyl itself, or other unidentified factors*". Further, the applicant claims that the GI toxicity seen in dogs is distinct from, and does not appear to be predictive of, nausea and decreased appetite observed in clinical trials with bardoxolone methyl. In summary, the mechanisms behind the toxicity observed in dogs have not been explained and it is not agreed that all toxicity seen in dogs (GI or other organs) should be disregarded.

3.2.4.1. Single dose toxicity

No single dose toxicity study has been submitted. This is acceptable.

3.2.4.2. Repeat dose toxicity

Mortality and Clinical signs

Significant mortality and severe clinical signs were reported from studies in mice, rats and hamsters.

In Syrian golden hamsters, daily oral administration of RTA 402 in a non-GLP study at dose levels of 3, 10, 30 and 100 mg/kg/day caused significant mortality, weight loss and toxicities in the two highest doses.

In mice, daily oral administration of RTA 402 at dose levels 5, 15, and 50 mg/kg/day for 28 days was associated with severe toxicity. Mortalities occurred in the 15mg/kg/day group starting on day 11. In the 50mg/kg/day, all animals were found dead, euthanized in extremis, or terminated early between day 5 through 7. Cause of death was considered to be multiple organ toxicity. Daily oral administration of RTA 402 in mice at 1.5 and 5.0 mg/kg/day in the 26-week repeat toxicity study was also associated with severe toxicity, and mortalities occurred at all dose levels. 28 animals were euthanized or found dead prior to the scheduled necropsy. 27 of these 28 animals had gross necropsy findings in the kidney including: kidney cysts or enlarged kidneys, pelvic dilation, necrosis tubular degeneration/regeneration, casts, and/or haemorrhage in males and females at both dose levels (1.5 and 5.0 mg/kg/day). Deaths of all animals that had kidney cysts or enlarged kidneys were considered RTA 402-related.

Daily oral administration of RTA 402 in rats for 28 days at dose levels 5, 10 and 20 mg/kg/day resulted in adverse findings at all dose levels and mortalities occurred at 10 and 20 mg/kg/day. Oral administration once daily for six months of RTA 402 in rats at dose levels 1/0.5mg/kg/day, 3/1.5mg/kg/day and 10/4.5mg/kg/day also caused significant toxicity and mortality. After 13 weeks of dosing, all dose levels in males were lowered to the same levels as the females. Hight dose males had

a five-day drug holiday before resuming on the lower dose. Mortalities included 5/35 males + 3/35 females at 3/1.5 mg/kg/day and 26/35 males + 24/35 females at 10/4.5 mg/kg/day. The causes of death were obstruction of the gastrointestinal tract, bone marrow depletion, or undetermined.

In beagle dogs, daily oral administration of RTA 402 at dose levels 2.5mg/kg/day, 12.5/7.5mg/kg/day and 20.0/12.5mg/kg/day caused significant toxicity and mortality. Four males at 12.5/7.5 mg/kg/day and five males at 25/12.5 mg/kg/day were euthanized in extremis due to poor physical health and severe weight loss. One female at 12.5/7.5 mg/kg/day and six females at 25/12.5 mg/kg/day were euthanized in extremis also due to poor physical health and severe weight loss.

Two pivotal studies were performed in cynomolgus monkeys with RTA 402: a 28-day repeated dose study to identify dose levels and a 12-month repeated dose study (dose levels 30/5mg/kg/day, 100/30mg/kg/day and 300mg/kg/day) with a 28-day recovery period. In the 28-day study, one control female died on day 25 due to dosing error. In the 12-month study, nine animals were sacrificed in extremis during the study. The sacrifice of six of these animals was attributed gavage error. Two animals had lung-related pathology suggestive of dosing error. The death of the last animal could be attributed GI perforation, possible from the mode of administration.

No mortalities were recorded in the dose-range finding study in minipigs and no mortalities were recorded in the 3-months once daily oral administration of RTA 402 in minipig at dose levels 6, 12, and 30 mg/kg/day.

Clinical signs and body weights

Clinical signs in the rodents (mice, rats, and hamsters) were similar. In mice, observations included decreased activity, weakness, convulsions, recumbency, increased respiratory effort, and/or animals cold to touch. Rats presented distended abdomen, discoloured hair, hunched posture, decreased activity, salivation, audible breathing, and cold to the touch in the two highest doses in the 28-day study. In addition, body weight and food consumption were lower compared to controls at all dose levels. In the 6-month study in rats, clinical findings included decreased activity, unkempt appearance, hunched posture, tremors, difficult and audible breathing, skin cold to touch, salivation, distended abdomen, material around the eyes, mouth, and/or nose, swelling in the lip and mouth, piloerection, white discoloured mouth, thinness, and extended penis. At the end of the recovery period, these clinical signs were no longer present.

Several beagle dogs were euthanized in extremis due to poor physical health and severe weight loss. Surviving animals lost weight, some considerable, and had markedly reduced food consumption, and exhibited clinical signs of thinness, yellow discoloured faeces, and a greater frequency of soft, watery, and mucoid faeces. The weight loss began early in the study and continued throughout the study. Many of these animals appeared to be in poor condition and general health because of the weight loss and poor nutrition.

In monkeys, clinical findings in the 28-days study included emesis sporadically across all groups. Inappetence in controls and at 25 an 75mg/kg/day. Soft and/or watery faeces across all groups with greater incidence in the treated group. Red anal discharge (1M), discoloured faeces (1M+1F) at 150mg/kg/day at week 4 evaluation. In the 12-months study, soft and/or watery faeces was noted across all groups this decreased during the 4-week recovery period. Body weights of treated males and females were lower compared to controls. No significant change in body weights was seen during the 4-week recovery period. Body weight gains during this time period were similar between control and treated animals.

In minipigs, a trend towards lower body weight gain in all treated groups was observed but did not reach statistical significance and food consumption was unaltered.

Tendency toward lower body weights in monkeys and in pigs is explained by the applicant by the pharmacological effect of the drug: Both genetic and pharmacologic activation of Nrf2 suppresses the expression of genes involved in fatty acid synthesis, including ATP-citrate lyase, fatty acid synthase, and stearoyl-CoA desaturase. Nrf2 activity also influences lipid accumulation in adipose tissue, as genetic or pharmacologic activation of Nrf2 in mouse models of obesity results in smaller adipocytes.

Ophthalmoscopic Examinations

In the 6-months study in rats at terminal examination (week 26), some males, and several females at 3/1.5mg/kg/day had conjunctivitis. Ophthalmoscopic Examinations in dogs and monkeys showed no test article-related abnormalities. In minipigs, some lenticular opacities were observed but these findings were not considered treatment related.

Haematology

In the 28-day study in mice, haematology evaluation was limited to only a few animals but showed decreases in platelet count lymphocyte count, reticulocyte count and lymphocyte count, and increases in neutrophils and monocytes. In the longer 26-weeks study in mice, no RTA 402-related effects were reported in either sex at any dose level. In the both studies in rats, numerous test article-related changes in haematology were observed at all dose levels. At the end of the 4-week recovery period, most of these parameters in the treated animals were essentially comparable to controls although a few parameters in the treated groups were still higher or lower than controls. Test article-related alterations in haematology values were observed in dogs including higher leukocyte, neutrophil, lymphocyte, and monocytes values, and lower erythrocyte, haemoglobin, and haematocrit values. In monkeys, no significant test article-related alterations in haematology values were seen in the 28-day study and only minor differences not considered to be toxicologically relevant were observed in the 12-month study. No significant test article-related haematology alterations were seen at the recovery interval of analysis. In the minipig, statistically significant changes in haematology parameters were observed. In females, mild dose-dependent decrease in RBCs (all treatment groups, week 6 and 13), haemoglobin (top dose week 6, top two doses week 13) and haematocrit (top dose week 6, all doses week 13). Similar trends were observed in the males. These changes were considered mild and not accompanied by clinical consequences such as pale or discoloured membranes.

A clinical OC has been raised regarding effects on haematopoiesis.

Clinical chemistry

Due to unobtained samples and early deaths in mice and sample volume limitations, assessment was limited to 4 males and 3 females administered 5 mg/kg and 3 males and 1 female administered 15 mg/kg and not all endpoints were assessed for all animals. Changes attributable to a hepatocellular and hepatobiliary effect included markedly increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activity, mildly increased alkaline phosphatase (ALP) activity (limited to animals at 50 mg/kg), and/or minimally to moderately increased total bilirubin concentration. Increased urea nitrogen, decreased total protein, albumin and globulin concentration was observed as well as decreased glucose and changes in triglyceride and cholesterol. No RTA 402-related effects were reported following administration up to 26-week. However, in mice euthanized early, there was mildly to moderately increased sodium with moderate to marked increases in phosphorus, SCr, and/or BUN.

In rats, RTA 402-related changes were observed including increases relative to control: AST, ALT, gamma glutamyltransferase (GGT), sorbitol dehydrogenase (SDH), total bilirubin, globulin, total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol values; decreases relative to control: ALP, albumin, and albumin/globulin (A/G) ratios in males and/or females at all dose levels. Similarly, in the 6-month study in rats, many haematology parameters

where significantly different from controls in males and females at all dose levels. After the recovery period, a few parameters in the treated groups were still different from controls.

In dogs, albumin values were lower in males and females at all dose levels. Several test article-related alterations were observed at 13 weeks in males and females including slightly higher compared to controls triglyceride values and slightly lower compared to controls bilirubin, urea nitrogen, creatinine, total protein, albumin, A/G ratio values, potassium values, and phosphorus values in females at the higher dose levels. One male at 25/12.5 mg/kg/day had significantly higher alkaline phosphatase, AST, ALT, sorbitol dehydrogenase, and cholesterol values compared to controls.

In monkeys, no significant test article-related alterations in clinical chemistry values were seen at the terminal evaluation in the 28-day study. In the 12-month study in monkeys, decreases were seen in cholesterol, total bilirubin, alkaline phosphatase, creatinine, blood urea nitrogen and AST. Other parameters were also changed but all changes in clinical chemistry were minor and not considered to be toxicologically relevant and not adverse. Most of the changes improved during the 4-week recovery period.

In minipigs, mild treatment related changes were observed at both Week 6 and Week 13 including decreases in ALAT, alkaline phosphatase, and triglycerides, increase in GGT in females, decreases in magnesium (M+F) and inorganic phosphorus in males, decrease in creatinine in females, a tendency toward higher globulin and a decreased albumin/globulin ratio, lastly some females had higher level of protein. The changes appeared to be without toxicologic consequence. After the 4-week recovery period, full recovery was observed in alkaline phosphatase, triglycerides, magnesium, phosphorus, and creatinine for the males and ALAT, triglycerides, and magnesium in the females. Partial recovery was observed for all other parameters.

A clinical OC has been raised regarding changes in bilirubin.

Urine analysis

No RTA 402-related alterations were observed in mice or in the 28-day study in rats. In the 6-month rat study, slight increases in pH were seen in the top two doses in females. In dogs, no test article alterations were observed at 13 weeks. One dog at high dose and one animal at mid dose had increased volume and lower specific gravity which was not considered test article related. No RTA 402-related alterations were reported in the 28-day study in monkeys. A trend towards increased urine volume and lighter colour was seen in minipigs.

Organ weights

In the 28-day study in mice, test article-related organ weight changes were present in the liver, adrenal glands, thymus, uterus with cervix, and right mandibular/sublingual salivary gland. In the 26-weeks study in mice, test article-related organ weight changes were present in kidney, ovary, uterus with cervix, prostate gland, liver, thyroid gland, spleen, thymus, and heart. In rats (28-day study), test article-related organ weight changes were present in liver, pituitary gland, thyroid/parathyroid glands, uterus with cervix, and thymus gland. In rats (6-months study) test article-related organ weight changes were present in liver, thyroid/parathyroid glands, kidney, liver thymus, spleen, thyroid glands and pituitary gland. In dogs, test article-related organ weight changes in surviving animals were present in liver, thymus, and adrenal gland. In monkeys, there were no definitive test article-related organ weight changes in the 28-day study. In monkeys in the 12-months study, liver, kidney, and spleen organ weights were higher than controls, and thymus weights were lower than controls after 6 and 12 months at most dose levels. Low thyroid gland weights were present in males at top two doses after 12 months. At day 382, liver and kidney weights were considered to be recovering and thymus weights recovered. All other organ weight differences were considered to be most likely incidental due to the lack of a dose response, the absence of correlative microscopic effects, the lack of similar

findings in both sexes, and/or based on the comparison of individual organ weight measurements from this interval to those measured at the interim and terminal necropsies. In the minipig, increased kidney weight was seen in the non-GLP 28-day study and increased kidney and liver weights were seen in the 3-month study with partial recovery.

Macroscopic findings

In mice, findings were present in the stomach (nonglandular and glandular), thymus, spleen, liver, testes, uterus with cervix, and adrenal glands. In the 26-week study in mice, 28 animals were euthanized or found dead prior to the scheduled necropsy. 27 of the 28 animals had gross necropsy findings in the kidney including: kidney cysts or enlarged kidneys, pelvic dilation, necrosis tubular degeneration/regeneration, casts, and/or haemorrhage in males and females at both dose levels (1.5 and 5.0 mg/kg/day). Deaths of all animals that had kidney cysts or enlarged kidneys were considered RTA 402-related. In the 28-day study in rats, findings included liver enlargement, nonglandular stomach thickening, decreased seminal vesicle size and decreased uterus size. In the 6-month study in rats, findings included cysts in the liver, enlarged liver, swollen/thickened nonglandular stomach, esophagus and lip, extended penis, body fat depleted, small ex-orbital lacrimal glands, small seminal vesicles, small spleen, and small thymus. These test article-related findings were generally increased in incidence and/or severity and were noted at lower dose levels at 6 months compared to 3 months. Following the recovery period, cysts in the liver and swollen/thickened nonglandular stomachs were the only test article-related macroscopic findings still present in males at 3/1.5 mg/kg/day and in females at 1.5 mg/kg/day. No animals were evaluated for reversibility at 10/4.5 mg/kg/day due to high mortality. In dogs, findings included thymus, body fat, stomach (pylorus), small intestine (duodenum, jejunum, and ileum), large intestine (cecum, colon and rectum), thoracic cavity, abdominal cavity, pancreas, and mesenteric lymph node. In monkeys, macroscopic changes seen after 6 months included small thymus in one male and severely small in one female. Two females had moderate body fat depletion. Multiple macroscopic findings were considered to be associated with gavage error. After 12 months, one female at high dose had a mildly small thymus. The spleen had tan focus/foci in 2 males at high dose and one female at mid dose. In minipigs, pale kidneys were described in one recovery female (12 mg/kg/day) and one recovery female (30 mg/kg/day).

Microscopic findings

In mice, test article-related microscopic findings were present in the heart, liver, gallbladder, oesophagus, stomach (nonglandular and glandular), small intestine (duodenum, jejunum, and ileum), large intestine (cecum and colon), testes, epididymides, seminal vesicles, ovaries, uterus with cervix, vagina, bone marrow (femur and sternum), adrenal glands, thymus, spleen, lymph nodes (mandibular and mesenteric), gut-associated lymphoid tissue (GALT), pancreas, salivary glands (submandibular and sublingual), harderian gland, and lung in the 28-day study. In the 26-week study in mice, histopathological findings were seen in kidney, ureter, bladder, female reproductive system, gallbladder, liver, thyroid gland, bone marrow, spleen, and heart.

In rats, microscopic changes involved liver kidneys, tongue, esophagus, nonglandular stomach, exorbital lacrimal glands, salivary glands, spleen, thymus gland, harderian glands, seminal vesicles, urinary bladder, vagina, and uterus in the 28-day study; and liver (cholangiomas, bile duct hyperplasia, biliary cysts, hepatocellular hyperplasia, and hepatocyte hypertrophy), squamous epithelium of the upper gastrointestinal tract (papilloma, basal cell and squamous cell hyperplasia), bone marrow depletion, kidneys (chronic progressive nephropathy and hyaline tubular casts), ovaries (interstitial cell hyperplasia) in the 6-month study. Findings were more severe in males and in higher doses. Findings increased in incidence at all dose levels at the 6-month interval compared to 3-months. However, bile duct hyperplasia, hepatocyte hypertrophy, basal cell hyperplasia in the nonglandular stomach, and renal changes were present at all dose levels at all time points. At the end of the

recovery period, no squamous cell papillomas were identified but basal cell and squamous cell hyperplasia, hyperkeratosis, and inflammation of the nonglandular stomach were still increased in incidence in males and females. Other test article-related findings in the glandular stomach, oesophagus, pharynx, and lips were considered reversible.

In dogs, microscopic findings were present in the kidneys, liver, adrenal glands, thymus, spleen, Peyer's patches, bone marrow (femur, rib and sternum), testes, epididymides, skin, oesophagus, stomach (cardia, fundus, and pylorus), small intestine (duodenum, jejunum, and ileum), large intestine (cecum, colon, and rectum), gallbladder, pancreas, lymph nodes (mediastinal and mesenteric), eyes, lung, salivary glands (mandibular, parotid, and sublingual), and skeletal muscle (biceps femoris).

The 28-day study in monkeys did not show any definitive test article-related microscopic changes. In the 12-months study, the gallbladder mucosa had hypertrophy/hyperplasia in males and females at all dose levels at 6 and 12 months. The liver had minimal inflammation surrounding the bile duct at 6 and 12 months primarily at high dose. Bile duct hyperplasia was present in the liver only at 12 months. Both the bile duct and gallbladder findings were reported by the applicant as non-neoplastic. The thymus had generalized lymphoid depletion at 6 and 12 months in males and females at mid and high dose. The spleen had congestion, generalized lymphoid hyperplasia, and follicular lymphoid hyperplasia at 12 months at mid and high dose. The cardia of the stomach and the rectum had erosion/ulceration at 6 months at mid and hight dose but not at 12 months. Decreased colloid was present in the thyroid gland at 12 months in males and females at mid and high dose. Many of these microscopic changes occurred in single animal of one or both sexes. At the end of the 4-week recovery period, test article-related microscopic findings were present in the liver of one male at mid dose and one male at high dose, consisting of minimal bile duct hyperplasia. The gallbladder and thymus were considered recovered after the 4-week recovery period. Spleen and thyroid changes were still present after the 4-week recovery period.

In minipigs microscopic findings were seen in GI tract (mild changes observed in both sexes in all treated groups included tongue, oesophagus, non-glandular stomach and small intestines characterized as an increased thickness of the squamous epithelium, involving mainly middle to outer portions. Elongation of villi was present in the small intestines), kidney (moderate finding: diffuse, global glomerulonephritis (1M 6mg/kg/day) glomerular change characterized as minimal/slight, multifocal/diffuse, segmental (involving only part of the glomeruli) glomerulonephritis (1 animal 30mg/kg/day + 2 recovery animals from 12mg/kg/day and 30mg/kg/day resp.), background levels of fibrosis, tubular basophilia, and interstitial inflammation, focal/multifocal fibrosis (some animals), minimal increase in Masson's trichrome and PAS-positive material in the mesangium (1F 30mg/kg/day + 1M recovery 30mg/kg/day). Recovery period: Full recovery: tongue, oesophagus, non-glandular stomach, jejunum, and ileum. Partial recovery: duodenum. Increased kidney weight was still observed in females, but partial recovery was observed for all other kidney parameters.

Kidney

Findings in the kidneys are of special concern given the proposed indication and patient population. Strikingly, 27/28 mice that were euthanized or found dead prior to scheduled necropsy in the 26-week study had gross necropsy findings in the kidney including: kidney cysts or enlarged kidneys, pelvic dilation, necrosis tubular degeneration/regeneration, casts, and/or haemorrhage in males and females at both dose levels. In addition, kidneys were affected in the minipig with changes present in all treatment groups. Increased kidney weight, although only statistically significant in males, was observed. A moderate diffuse proliferative glomerulonephritis was observed in one male. A similar glomerular change was reported in three other animals, however, described as minimal/slight, multifocal/diffuse, segmental glomerulonephritis. Urine volume was increased, creatinine was

decreased in all dose groups for females with similar trend in males. applicant states that kidney effects in minipigs are exacerbations of spontaneous glomerulonephritis in this species, which is acknowledged, but taking into consideration that bardoxolone's target organ is kidney, treatment effect cannot be excluded. In dog, minimal to mild tubular dilatations and degeneration/regeneration were present at all doses. In the monkey, occasional kidney findings were reported.

GI-tract

GI-tract findings were reported from all species. Mice, rats, hamsters, and monkeys were administered sesame oil (vehicle) or RTA 402 as a suspension in sesame oil. Emesis and soft or watery faeces were observed in most groups, and according to the applicant, these clinical findings could partially be attributed to the sesame oil, but the applicant has not explained how the sesame oil would cause these clinical findings. Importantly, there are finding supporting that RTA 402 itself causes GI toxicity. In the 28-day study in monkeys, soft and/or watery faeces was noted with greater incidence in the treated group. In the oral embryo-foetal and postnatal development study in monkeys (RTA402-P-1101), the animals did not receive sesame oil, but all test item-treated groups showed liquid or soft faeces. The number of affected animals and the intensity of the signs of diarrhoea showed a clear dose-relationship. Minipigs and dogs did not receive the sesame oil in the repeat dose studies. In minipigs, minimal-slight changes were reported in the tongue, oesophagus and non-glandular stomach and was characterized as an increased thickness of the squamous epithelium, involving mainly middle to outer portions. Elongation of villi was present in the small intestines. The dog displayed extensive GI-toxicity with microscopic findings in stomach (cardia, fundus, and pylorus), small intestine (duodenum, jejunum, and ileum) and large intestine (cecum, colon, and rectum). The GI tract is of particular concern given the AEs reported in the clinical trials.

Reproductive organs

Findings on reproductive organs are discussed in the reproductive and developmental toxicity section.

Heart and Electrocardiographic examinations

In the 26-week study in mice, a microscopic finding of uncertain relationship to test article administration was present in the heart. One male administered 5 mg/kg/day that survived to the scheduled early terminal necropsy on Day 155 had minimal myofiber degeneration/necrosis in the heart. One male administered 5 mg/kg/day that was euthanized in extremis on Day 152 had mild myofiber degeneration/necrosis in the heart. Myofiber degeneration/necrosis can be a feature of rodent progressive cardiomyopathy, a common background finding in aging rodents. While the incidence was low in this group, similar findings were not present in controls in this study. Some heart microscopic pathology findings were also reported in the 28-day study in mice and was graded as minimal to moderate.

Regarding electrocardiographic examinations, no abnormalities were reported from dogs or monkeys. In the minipig, no treatment related effects were reported. However, the P-wave was statistically significantly longer in 12 mg/kg/day-group females after 13 weeks of treatment, although the applicant argues this finding was not adverse due to no dose-related effect and that there were no other changes in the ECG.

Findings on cardio parameters were present in the safety pharmacology studies. See relevant section for further discussion and OC.

Liver

Macroscopic and microscopic changes in the liver were reported in mice. In rats, macroscopic changes such as cysts in the liver and enlarged liver; and microscopic changes such as cholangiomas, bile duct hyperplasia, biliary cysts, hepatocellular hyperplasia, and hepatocyte hypertrophy were reported.

In dogs, increased liver weight and minimal to mild panlobular hepatocellular hypertrophy (males) and minimal to mild Kupffer cell hypertrophy/hyperplasia and/or minimal acute inflammation were reported.

In the 12-month study in monkeys, test article-related findings included minimal to mild biliary hyperplasia and minimal biliary inflammation (100/30 and 300 mg/kg/day). Increased liver weight was also noted. The applicant argues that the hepatobiliary changes should be considered not adverse based on the minimal to mild nature, lack of clinical pathology alterations and partial or complete recovery by 28 days post treatment. However, it should be noted that at the end of the 4-week recovery period, test article-related microscopic findings were still present in the liver of one male at 100/30 mg/kg/day and one male at 300 mg/kg/day (consisting of minimal bile duct hyperplasia). It should also be noted that increases in liver enzymes were present in clinical studies.

Increased liver weight was also noted in the minipig.

Spleen, thymus and immunotoxicity

In the 12-month repeated oral dose study in cynomolgus monkeys, test article-related increases were noted in the relative percentage and absolute counts of monocytes and B lymphocytes in the 100/30 and 300 mg/kg/day dose levels in males and females. Females exhibited decreases in the relative percentage of mature T cells and CD4+ T cells at 6 and 12 months. Males at all dose levels did not show significant changes in relative percentages and absolute cell counts of CD4+ T cells and CD8+ T cells at 6 and 12 months but did show significant decreases in the percentage of mature T cells at 6 and 12 months. In addition, the thymus had generalized lymphoid depletion at Days 186 and 354 in males and females at 100/30 and 300 mg/kg/day and the spleen had congestion, generalized lymphoid hyperplasia, and follicular lymphoid hyperplasia at Day 354 at 100/30 and 300 mg/kg/day. The NOAEL mg/kg/day corresponded to approximately 3 times the clinical exposure. Effects on thymus were also seen in the rodent and dog studies (reduced thymus weight with concomitant lymphoid depletion).

Long term effects

The carcinogenic potential of bardoxolone methyl has not been studied in animals, however, repeated-dose studies can be used to provide some insight into long term effects of bardoxolone methyl exposure. 26-week study in mice revealed kidney cysts in several animals and an oesophagus mass in one animal. 6-month study in rats showed cysts in the liver with correlating microscopic findings such as cholangiomas, bile duct hyperplasia, biliary cysts, hepatocellular hyperplasia, and hepatocyte hypertrophy and swollen/thickened nonglandular stomachs which remained after 4-week recovery period. The 12-months study in monkeys did not reveal any tumours but some organs showed hyperplasia (gallbladder and liver bile duct (reported by the applicant as non-neoplastic), spleen follicular lymphoid). At the end of the 4-week recovery period, test article-related microscopic findings were present in the liver of two males, consisting of minimal bile duct hyperplasia. The gallbladder was considered recovered after the 4-week recovery period while spleen changes were still present. The dogs also displayed hyperplasia in different organs. In the 3-months study in minipigs, elongation of villi was present in the small intestines. Full recovery was observed in jejunum and ileum, partial recovery in duodenum.

3.2.4.3. Genotoxicity

A battery of genotoxicity tests was performed including two Ames test with both rat and human S9 fractions, one *in vitro* mammalian chromosome aberration assays with Chinese hamster ovary (CHO) cells, two *in vitro* mammalian chromosome aberration assays with human peripheral blood lymphocytes (HPBLs) using rat and human S9 fractions, respectively and one *in vivo* micronucleus test using bone marrow smears of cynomolgus monkeys.

The Ames test was negative for genotoxicity. The *in vitro* chromosome aberration assay using CHO cells had a positive clastogenic signal, whereas the HPBLs assays were negative for clastogenicity. The positive CHO cell results need further discussion. The *in vivo* micronucleus test in cynomolgus was negative.

3.2.4.4. Carcinogenicity

The carcinogenic potential of bardoxolone methyl has not been studied in animals and the long-term effects of bardoxolone methyl on the carcinogenicity risks remain unknown. Standard non-clinical carcinogenicity models would not provide relevant information on the carcinogenicity of bardoxolone methyl, due to major differences in metabolism resulting in severe toxicity. The lack of carcinogenicity studies is therefore acceptable.

The applicant has provided a weight of evidence discussion on the carcinogenic potential of bardoxolone methyl which indicates that there is no clear concern of cancerogenic risk. However, it should be noted that the literature indicates a dual role of Nrf2 in cancer biology. On the one hand, Nrf2 has been associated with anti-tumour effects in various animal models. However, there are also publications supporting that constitutively active and unregulated Nrf2 promotes survival advantages and confers resistance and that Nrf2 inhibition would be beneficial when treating tumours. Given the apparent dual role of Nrf2 in cancer, the applicant is asked to consider including malignancy as a potential risk in the RMP.

3.2.4.5. Reproductive and developmental toxicity

The reproductive and developmental program for bardoxolone methyl consists of pilot embryo-foeal development (EFD) studies in rats and rabbits, a dose-range finding (DRF) study in minipig and an enhanced pre- and postnatal development (ePPND) in monkeys. No Fertility and early embryonic development (FEED) studies were conducted.

FEED

No stand-alone FEED studies have been performed. Evaluation of male and female reproductive organs was performed in the repeated-dose toxicity studies in mice, rats, dogs, minipigs and cynomolgus monkeys.

In general, several findings on reproductive organs were reported in mice, rats and dogs, while monkeys and minipigs did not show any effects on the reproduction organs at exposures corresponding to approximately 3 times (monkey) and 2 times (minipig) the estimated human exposure levels. The applicants claim that the testis findings in dogs are not relevant due to severe GI toxicity need further discussion. Moreover, the monkeys used in the 12-month repeated-dose study were juvenile and not sexually mature and therefore the reproduction organ data from monkeys is considered of limited value.

EFD

Pilot EFD studies in rats and rabbits

A pilot GLP EFD study was conducted in rats which showed maternal and developmental toxicity from 5mg/kg/day.

In rabbits, maternal toxicity (decreased weight gain and abortions) was evident from 5 mg/kg/day. Foetal toxicity (lower foetal weight) was seen from 10 mg/kg/day. At 10mg/kg/day there was increased post-implantation loss vs control (17,4% vs 6,2%). No increase in post-implantation loss was observed at 20 mg/kg/day.

DRF in minipigs

A GLP dose-range finding EFD study was conducted in Göttingen minipigs. Maternal effects on body weight gain, coupled to decreased food intake were observed. Increased early resorptions, increased post-implantation loss, reduced uterus weight and decreased number of live foetuses were seen when compared to control animals. Moreover, decreased foetal weight was also observed and associated with decreased placenta weight and decreased nose-to-tail head length compared to the control group.

Foetal effects/malformations were also observed in minipigs. Foetal angulated tails were seen in all doses but not in controls. Moreover, increased number of digital malformations (polydactyly, syndactyly and associated misshapen digits) were seen in foetuses from mid and high dose mothers. The above findings in the DRF minipig study needs further discussion.

ePPND study in monkeys

The ePPND study in cynomolgus monkeys evaluated the potential effects of bardoxolone methyl on pregnancy, embryo-foetal developmental, parturition and lactation, as well as survival, growth, and postnatal development of the offspring up to 6 months after birth.

Bardoxolone methyl exposure in pregnant monkeys was well tolerated. The highest dose level (30 mg/kg) which also was the NOAEL for embryonic/foetal development resulted in approx. 2,5 times exposure margin to human dose based on AUC.

Dose dependent GI toxicity (diarrhoea) was observed in all maternal animals. High-dosed mothers showed lower body weight gain. This effect was seen later in the pregnancy (after GD 100), was reversible in lactating females and most likely coupled to the observed diarrhoea. Maternal weight effects are mentioned in section 5.3 of the SmPC. Maternal necropsy did not reveal any findings related to treatment.

No significant effects of bardoxolone methyl exposure on pregnancy outcome parameters were noted. No clear significant effects on foetal data including body weights, body measurements, or external, visceral, and skeletal examinations were observed. However, there was an observation within the low dose group of one foetus showing decreased head width, which was a result of multiple skeletal malformations within the skull (flattened frontal, bilateral enlarged orbital, fused and narrowed nasals and fused and shortened maxillae) Given it occurred at the lowest tested dose and was a single occurrence, it is considered unlikely to be treatment-related.

Pups of high dosed mothers showed reduced birth weights (approx. -16 %) whereas their body weight gain was comparable to pups from control mothers resulting in a slightly (-6%) lower body weight at PND 168. The infant weight effects are described in SmPC 5.3. Coupled to this, absolute organ weights from the pups of high dosed mothers were slightly decreased while organ/body weight and organ/brain weight ratios were comparable to control animals.

Morphological examinations, neurobehavioral testing, and the grip strength test did not reveal bardoxolone methyl-related differences between infants of the dose groups and control infants.

Based on the exposure in pups on PND 1 it seems likely that placental transfer occurs. Moreover, bardoxolone methyl was dose-dependently present in the milk of lactating monkeys on PND 28, indicating that the pups were exposed via breast feeding.

Juvenile toxicity

Although bardoxolone methyl is indicated for the treatment of chronic kidney disease (CKD) caused by Alport syndrome in adults and adolescents aged 12 years and above, no dedicated juvenile toxicity studies have been performed. The clinical trials in Alport syndrome included patients from age 13-70 years, and in total 32 patients under the age of 18 years have been dosed in clinical trials.

3.2.4.6. Toxicokinetic data

Exposure margins from NOAEL in non-clinical studies to human clinical exposure ranged between 0.5-3.1 for AUC and between 0.4-4.7 for C_{max}. It should be noted that systemic exposures in monkeys were not dose proportional, on the contrary, exposure was actually higher at lower doses. A similar situation was observed in the minipigs.

3.2.4.7. Tolerance

No studies have been conducted. The intended route of administration is oral. The gastrointestinal tract was evaluated in all repeat-dose toxicology studies. Specific studies were not considered necessary.

3.2.4.8. Other toxicity studies

Immunotoxicity

Immunotoxicity was evaluated within the 12-month repeated oral dose study in cynomolgus monkeys. Peripheral blood leukocyte analysis showed test article-related changes in the relative percentage and absolute cells counts of monocytes and B cells at 100/30 and 300 mg/kg/day. Females exhibited decreases in the relative percentage of mature T cells and CD4+ T cells at 6 and 12 months. Males at all dose levels did show significant decreases in the percentage of mature T cells at 6 and 12 months. No test article-related changes in the mean relative percentage or absolute cell counts of CD8+ T cell, and NK cells were observed in males or females. In addition, the thymus had generalized lymphoid depletion at Days 186 and 354 in males and females at 100/30 and 300 mg/kg/day and the spleen had congestion, generalized lymphoid hyperplasia, and follicular lymphoid hyperplasia at Day 354 at 100/30 and 300 mg/kg/day. The NOAEL mg/kg/day corresponded to approximately 3 times the clinical exposure.

Phototoxicity

Bardoxolone methyl absorbs no or minimal light in the in the wavelength of 290-700nm. The Aplicant states that molar extinction coefficient (MEC) at 290 nm was 90 L mol^{-1} cm^{-1} (below the threshold of 1000 L mol^{-1} cm^{-1}) hence further investigations are not considered warranted at this time point. applicant is invited to present the Report on determination of MEC.

Mechanistic in vitro studies with metabolites

Cholestasis

Given the rodent specific metabolism resulting which the applicant considers to result in rodent specific toxicity, the applicant has performed mechanistical *in vitro* studies in rat, monkey, and human hepatocytes investigating effects of Bardoxolone methyl and C17-carboxylic acid metabolite RTA 401 on bile acid secretion. The effect of bile acid excretion was evaluated with the hepatocellular disposition of carboxydichlorofluorescein (CDF) analysed by fluorescence microscopy, and cytotoxicity was evaluated by AST, ALT and LDH levels in the culture medium. According to the applicant, Bardoxolone methyl and RTA 401 showed excretion of CDF into the bile lumen at 0,1 µmol/L in all species, and intracellular accumulation was seen at 10 µmol/L in all species. At 1µmol/L, CDF accumulation, an index for cholestasis, was only observed in rat hepatocytes.

mRNA expression profile

In vitro gene expression of Nrf2 regulated genes and bile acid related genes was analysed by quantitative real-time PCR cultured rat and human hepatocytes. Expression of bile acid transporter bile salt export pump, BSEP, was either increased or unchanged in human hepatocytes whereas the expression was supressed in rat hepatocytes when treated with RTA 402 and RTA 401 after 24h treatment. The applicant states that BSEP is considered to play a main role in bile acid efflux.

in silico evaluation-QSAR

An ICH M7 compliant toxicological analysis for bacterial mutagenicity using literature review and/or in silico evaluation was conducted on potential impurities. All studied compounds (39 structures) were classified as non-mutagens.

A concern is raised in the quality part regarding impurities 1,2-Dihydro RTA402 and iso-isoxasole which are not considered qualified at this time point.

3.2.5. Ecotoxicity/environmental risk assessment

The refined Phase I PECsw value for bardoxolone methyl is 0.003ug/L, not triggering a Phase II risk assessment. The refinement was based on an Fpen value of 2/10000 (or 0.0002) which is based on the official EMA Orphan designation document (EMA/266267/2018) that relates to an EU-population of 517,400,000 (Eurostat 2018). The log Kow for bardoxolone methyl, determined at 25 ± 0.5 °C by the slow-stirring method, was >5.17.

Summary of main study results

Substance (INN/Invented Name): Bardoxolone methyl			
CAS-number (if available): 218600-53-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD TG123	>5.17	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	>5.17	B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement:	PBT status cannot be concluded without PBT screening.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
Fpen refined Phase I PECsw (based on prevalence)	0.003	µg/L	> 0.01 threshold (N)
Other concerns (e.g., chemical class)			(N)

3.2.6. Discussion on non-clinical aspects

Pharmacology – Primary pharmacodynamics

A basket of *in vitro* studies is presented to characterize the pharmacodynamic effects of BM, spanning from Nrf target gene expression, restoration of mitochondrial dysfunction and reduction of proinflammatory signalling. In summary, the *in vitro* studies support the suggested pharmacological rational. However, the MoA for this transcriptional Keap1/Nerf2-pathway appears complex and which specific mechanistic process that would indeed be active and to what relative extent in relevant tissues in a treated Alport patient is difficult to predict. It is noted that no IC50 value for BM binding to its target, Keap1, is provided. The IC50 values presented is based on an *in vitro* assay for IFNγ-induced nitric oxide production in RAW 264.7 macrophages, which was used for a study where the pharmacological activity of BM was compared to BM metabolites (resulting in a IC50 range of 1.9-7.9 nM). Neither is any *in vitro* characterisation of BM pharmacological activity in tox-species presented**.**

There is some uncertainty whether bardoxolone methyl or bardoxolone is the active substance. It is important to clarify whether the active substance is bardoxolone (presently approved INN) OR bardoxolone methyl (ATC code applied for in Aug 2021) and whether the pharmacological

activity/properties are attributed to the methyl group as well and not only the bardoxolone compound. The outcome from the ATC code application should be reported and the actual substance that is put forward as the active moiety should be justified.

The ability of BM to trigger Nrf2 prototypical target gene expression *in vivo* at the mRNA and the protein level in the kidneys was demonstrated in cynomolgus monkeys, including elevated renal protein expression of NQO1, primarily localized to tubules and increases in corresponding enzyme activity and increased renal concentration of endogenous antioxidant Glutathione (GSH). Overall, these data demonstrate that BM induces pharmacologic activation of Nrf2 in the kidneys, including decreases in serum creatinine and blood urea nitrogen (BUN), and increased creatinine after oral dosing in nonhuman primates. In addition, no to minimal histological evidence of structural damage to the kidney was observed after 12 months of daily administration. Worth noting, no chronic kidney disease or proinflammatory condition to be corrected was present in these healthy animals that were treated.

Induction of the antioxidative enzyme Nqo1, responding downstream to Nrf2 activation, was confirmed in mice. BM treatment increased the mRNA and protein levels of Nqo1 in the renal cortex of wild-type but not Nrf2-null (Nrf2-/-) mice. The absence of response in the in the Nrf2-null mice indicates that the Nqo1 response is Nrf2 dependent. In the same study, a transcriptomic analysis of kidney tissue indicated that BM regulates the expression of genes involved in renal homeostatic processes, including Nrf2-mediated oxidative stress response, glutathione-mediated detoxification, and pentose phosphate pathway signalling.

According to the applicant, toxic metabolites are formed in rodent species and therefore very limited investigations have been carried out with BM, restricted to low dose and short treatment duration, in rodent models. Due to these species-specific metabolites, suggested to cause toxicity in rodents, though not clearly shown not to be caused by BM itself, structural analogues to BM have been used as surrogates to investigate the pharmacology of Nrf2 activation in kidney disease models. The used structural analogues lack the methyl ester moiety at the C17 position and therefore do not form toxic C17-carboxylic metabolites. This strategy is based on that the structural analogues and BM share the pharmacophore and pharmacological activity.

The applicant present a high-level list of eight studies along with general findings demonstrating that analogues (and in some case BM) are active in multiple kidney disease models. For three of the listed studies more details were presented. In the ICGN mouse model of nephrotic syndrome, RTA dh404 treatment resulted in e.g. suppressed inflammation associated with decreased kidney fibrosis (SCr), reduced blood urea nitrogen (BUN) and increased number and improved ultrastructure of mitochondria. In the 5/6 nephrectomy model of hyperfiltration-induced chronic renal failure in rat, RTA dh404 treatment resulted in e.g., decreased pressure-mediated glomerulosclerosis, tubulo-interstitial injury, inflammatory cell infiltration, and fibrosis, along with decreased markers of oxidative/nitrosative stress and inflammation. In a protein-induced nephropathy model in uni-nephrectomized mice with protein overload-induced interstitial inflammation and fibrosis, RTA 405 resulted in decreased levels of interstitial inflammation and decreased fibrosis. Overall, these studies with structural analogues indicate that the BM analogues may target various structural processes that contribute to irreversible kidney function loss. The suggested MoAs could be valid also for BM, provided BM shares the same pharmacophore and pharmacological activity with the structural analogues.

BM treatment cause an increased eGFR in clinical studies. An increased eGFR could be caused by an increased blood pressure or pressure over the glomeruli that subsequently could lead to glomeruli damage. However, the applicant claims the observed increased GFR can be explained by BM acting by "Novel mechanisms" not dependent on increased pressure over the glomeruli. Support for their view is provided by a set of studies conducted with BM or structural analogues, indicating that the increase in GFR may be explained by such "Novel mechanisms" i.e., BM may act by an effect on glomerular

surface area; or by an effect on Angiotensin II-induced mesangial cell contraction causing glomeruli volume changes; or by a reduction of endothelial dysfunction; and not by increasing systemic or intra-glomerular blood pressure.

In vivo multiphoton microscope (MPM) imaging in mice treated with the BM analogue RTA dh404 resulted in increased single-nephron GFR (SNGFR), and as the applicant claims, with concomitant increasing glomerular volume without changes in blood pressure. However, in Figure 14, *Pharmacology Written Summary*, a significant difference in glomerular volume is only indicated between Keap1-KD vs. WT but not for WT+RTA404 vs WT. The discrepancy between the shown data and the conclusions should be clarified. Moreover, the statement on no change in blood pressure is not supported by any shown data. These data should be provided, or the statement adjusted accordingly. In addition to the increased NNGFR, no significant alterations were observed in glomerular afferent/efferent arteriole ratio or the glomerular permeability of albumin and 40 kDa dextran. In conclusion, the increase in GFR appeared not associated with changes in glomerular permeability of albumin or with changes in afferent/efferent arteriolar ratios, providing support for a MoA not associated with increased intraglomerular pressure. These changes were not observed when the BM analogue was administered to Nrf2-null mice, indicating the critical importance of Nrf2 for the increases in SNGFR. It is noted, the provided reference, Kidokoro, 2019a, is a meeting abstract offering limited possibilities for assessment. Also, it appears to not show any systemic blood pressure measurement values. Moreover, in contrast to what is referred to as source in Figure 14, for results from RTA dh404 treatment, Kidokoro 2019b does not describe data from studies with RTA dh404 treatments but other non-bardoxolone related agents.

The contractile state of mesangial cells in the glomeruli affect the glomeruli volume and thereby the available glomerular surface area for filtration which also affect the GFR such as less contracted mesangial cells will lead to increased glomeruli volume and surface area which in turn lead to an increased GFR. Evidence for that BM and related analogues can affect the contractile state of mesangial cells and increase the glomerular surface area for filtration was provided by showing a decrease in ex vivo angiotensin II induced contraction of human mesangial cell in a concentration- and time-dependent manner after ex vivo BM exposure. Furthermore, glomeruli from rats treated with BM analogue RTA 405 were resistant to angiotensin II-induced contraction ex vivo. Rats treated with RTA 405 also showed a reversal of the angiotensin II-induced reduction of inulin clearance as well as increased the basal GFR levels, indicating increased GFR. This occurred without any changes in blood pressure or renal plasma flow. Overall, this demonstrates that the RTA 405 BM analogue can reverse angiotensin II-mediated impairment of the glomerular surface area (Kf), which may also apply to BM and, if so, this mechanism may contribute to the observed BM-induced GFR increase observed in the clinical trials.

Support for possible MoAs for how BM may reduce endothelial dysfunction in CKD was also presented. The impaired vasodilatory response to acetylcholine in the rat 5/6 nephrectomy model of hyperfiltration-induced chronic renal failure was restored by RTA dh404 treatment. In addition, the impaired Nrf2 content in the nucleus, as well as Sod2, Ho-1, and Keap1 protein expression, associated with the model, was normalized by the RTA dh404 treatment. It was also shown that BM can decrease ROS and increase endothelial NO in a dose-dependent manner in human umbilical vein cells (HUVECs). The suppression of ROS and induction of endothelial NO was attenuated when Nrf2 levels were decreased with siRNA, indicating that the effects were mediated through Nrf2. In summary, the presented results show possible MoAs for how BM may reduce endothelial dysfunction in CKD.

Overall, the *in vivo* and ex vivo studies conducted with structural analogues indicate that the BM analogues may target various structural processes that contribute to irreversible kidney function loss and provide support for the "Novel mechanisms" not dependent on increased pressure over the glomeruli. Although the studies have been carried out mostly with BM analogues, the suggested MoAs

could be valid also for BM, provided BM and the used structural analogues shares the same pharmacophore. However, it is questioned whether the claimed positive effect on kidney function can be maintained over time in patients with Alport syndrome. The applicant should provide a thorough scientific discussion based on available literature to support that the claimed positive effect on kidney function in patients with Alport syndrome can be maintained over time. In specific, the applicant should justify that long-term Nrf2 activation – or other bardoxolone- mediated effects- does not have a negative impact on kidney function over time.

Pharmacology – Secondary pharmacodynamics

Off-target activity of BM was evaluated *in vitro* to a panel of 43 receptors, ion channels, transporters, and enzymes. At a concentration of 10 µM, BM significantly inhibited reference compound binding (>50%) to the D1 dopamine receptor (55.7%) and the CB1 cannabinoid receptor (58.8%). However, at 1 µM, BM did not significantly inhibit any reference compound receptor binding or enzyme activity. The *in vitro* concentration of 1 µM BM corresponds to approximately 500 times the mean maximum steady-state unbound drug plasma concentration (Cmax) in Alport syndrome patients administered the MHRD (30-mg, PO). Thus, no off-target activity was observed for BM. Nevertheless, considering the electrophilic nature of BM and the number of safety related findings, screening of only 43 potential off-targets may have been at the lower end.

Because of the wide spectrum of effects that inhibition of KEAP1 and the subsequent activation of Nrf2 may trigger, involving transcription of numerous genes that collectively is involved in the regulation of the redox balance, mitochondrial function, inflammation and metabolic reprogramming, bardoxolone treatment can be expected to induce a wide set of pharmacological effects affecting multiple physiological processes. In the context of secondary pharmacodynamics, the applicant discuss a number of such Nrf2/KEAP1 associated physiological (and pathophysiological) processes that are affected by BM treatment and associated with the present CKD indication. A vast literature in conjunction with some studies conducted by the applicant or associates are presented as *"Additional Pharmacological Characterization"* related to findings in nonclinical toxicity and clinical studies. Some of these findings are described as undesirable effects in the SmPC (i.e., reduced body weight, increased BNP and elevated aminotransferases). Overall, the applicant put forward that several of the observed potential adverse effects may be driven by the pharmacological effect by BM on Nrf2 activation and not by general toxicity as summarized below.

Due to that increased liver weights and biliary hyperplasia were observed in the pivotal toxicity studies in monkeys and minipigs, a study was conducted in rats with the BM analogue RTA dh404 to investigate the pharmacological basis for these BM associated effects. Activation of Nrf2 is expected to increase hepatic GSH concentrations, which is involved in the regulation of the bile flow. Increases in hepatic GSH content result in increased bile flow, while depletion of GSH decreases bile flow. Approximately half of the bile flow depends on hepatically-derived GSH. This suggested mechanism is supported by the fact that genetic activation of Nrf2 through knockdown of Keap1 in mice results in significant increases in the hepatic mRNA expression of GSH synthesis genes, and a 35% increase in bile flow with an accompanying 43% increase in the biliary excretion of GSH without affecting the biliary excretion of bile acids (Reisman, 2009). In accordance with the suggested mechanism, treatment with RTA dh404 dose-dependently increased bile flow and biliary excretion of GSH. In contrast, RTA dh404 did not impact biliary excretion of bile acids. In accordance with Reisman 2009, the choleretic effects of RTA dh404 appear to be due to increased GSH concentrations. The applicant interprets these collective findings as suggestive of that the liver effects (increased liver weights, minimal biliary ductule hypertrophy, and hyperplasia in conjunction with decreased serum bilirubin) observed in the GLP toxicity studies in monkeys may be a consequence of bardoxolone methyl pharmacology. However, although a BM analogue induced dose-dependent increase in bile flow and biliary excretion of GSH occurred and that a similar observation was made also in Keap1 KO mice, thus

indicating a Nrf2 dependent mechanism, increased liver weight and biliary hyperplasia may also involve other mechanisms. Regardless of mechanism, it is of importance to understand whether BM-mediated liver and biliary effects such as biliary hypertrophy and hyperplasia could be adverse in the long-term. This has been further addressed in the clinical safety section, with several related questions (e.g. OCs 140- 144).In addition, biliary hyperplasia should be taken into account when considering the BM effects on tumor cells (further details in the tox section).

The observation of BM associated reduced body weigh were discussed in the context of a wide literature describing that both genetic and pharmacologic activation of Nrf2 affects key metabolic body weight associated pathways. Thus, it is possible that BM treatment have pharmacological metabolic effects of which the observed reduced body weight may be an outcome.

BM treated Alport patients showed increases (mild to moderate) in serum levels of brain natriuretic peptide (BNP) and N-terminal pro-peptide equivalent -BNP (NT-proBNP), (as noted in SmPC 4.8). In the literature several studies have demonstrated that weight loss induced by dietary intervention, bariatric surgery, and/or exercise programs correlates with a small, but significant, increase in circulating BNP levels, indicating that BNP levels can be positively influenced by changes in body weight and associated metabolic parameters. Based on these observations, the applicant hypothesized that the small increase in BNP observed following treatment with BM in the clinic could be a marker of metabolic reprogramming associated with increased fatty acid oxidation and energy expenditure. To test this hypothesis, a study was conducted in mice fed a high-fat diet for 12 weeks to assess the effects of 2 different BM analogues. The key result, that cardiac Nqo1 mRNA expression, a measure of Nrf2 activity, and a observed prevention of weight gain correlated with significantly higher levels of BNP (Nppb) expression in the heart. These results were in accordance with the hypothesis.

In patients with Alport syndrome, BM was associated with mild to moderate, reversible elevations in serum aminotransferase activity, which is noted in SmPC 4.8. Although serum aminotransferase activities increase following tissue damage, the applicant put forward that ALT and AST have important and complex physiological roles, and that these enzymes are not simply biomarkers of hepatic injury. Several studies were carried out to illustrate the association of Nrf activation to changes in transaminase levels and that BM can regulate aminotransferase gene expression also in extrahepatic tissues. In mice, genetic activation of Nrf2 (Keap1-knockdown) increases hepatic and renal ALT mRNA levels, whereas genetic deletion of Nrf2 (Nrf2-null) decreases them, with correlative serum levels of ALT protein. Exposure of cultured cells derived from liver, colon, skeletal muscle, macrophages, and proximal tubule to BM results in concentration-dependent increases in both ALT and AST mRNA levels. In addition, increases in aminotransferase levels have been associated with several conditions that affect cellular metabolism and energy production. Increase in aminotransferase expression can be observed at the transcriptional level in human hepatocytes without affecting cellular viability (Thulin, 2008; Josekutty, 2013). Moreover, aminotransferase activity detected in the serum is presumed to be due to the release or leakage of aminotransferase enzymes from their tissues of origin; however, the exact mechanism of the release is not understood. However, there is evidence to suggest that release of ALT and AST from cells can occur in the absence of any cellular toxicity *in vitro* (Josekutty, 2013). The current biochemical assays used to measure serum ALT and AST activity are incapable of determining from which tissue(s) the enzymes were released. Moreover, the nature of the assays does not allow discernment between the activities derived from cytoplasmic (i.e., ALT1 and AST1) versus mitochondrial (i.e., ALT2 and AST2) isoforms. For example, both hepatic injury and muscle injury, due to strenuous exercise, increase serum ALT activity; however, ALT1 is responsible for the increase in activity following hepatic injury, whereas ALT2 is responsible following muscle injury (Rafter, 2012). The applicant suggest that these data collectively indicate that Nrf2 and bardoxolone methyl regulate transcription of ALT and AST and suggest that the transient increases in transaminase levels observed in BM treated patients may be related to the pharmacology of the drug and not necessarily liver

toxicity. To conclude, it is acknowledged that the physiology and pathophysiology in this context is complex. The reasoning can be followed, and it is agreed that the clinical findings is not necessarily related to liver toxicity, however it can neither be entirely excluded.

A transient increase in albuminuria (assessed as urine albumin-to-creatinine ratio (UACR)) have been observed in clinical trials with BM. Albuminuria is used as a measure of kidney function and an increase can be an indication of reduced glomerular integrity and endothelial dysfunction. A chronically increased intraglomerular pressure is harmful to the filtration barrier and could be driving such a kidney damage. However, the applicant presents a number of findings to demonstrate that the BM treatment induced increase in albuminuria is a reversible pharmacological effect related to increases in eGFR and reduced protein reabsorption in the proximal tubules, and not the result of irreversible kidney damage. The results from the multiphoton microscopy study of maintained fluorescence-labelled albumin permeability in conjunction with an increased SNGFR together with the downregulation of the albumin transporter megalin in proximal tubules of BM treated monkeys demonstrates that albuminuria can occur in response to BM treatment without concomitant reduced glomerular integrity.

In addition, *in vitro* and *in vivo* studies were conducted to evaluate the effects of BM (and/or analogues) on the endothelin signalling pathway in search for an explanation of the BM associated findings of congestive heart failure (CHF) secondary to fluid overload in Type 2 diabetic patients with Stage 4 CKD. However, although extensively described, the beneficial effect is not entirely clear to the assessor, as a reduced ET1 signalling appears both causing the fluid overload with subsequent congestive heart failure and being suggested as a beneficial effect behind BM treatment. Furthermore, the studies and reasoning are not reflected in the applicant's Nonclinical overview.

To summarize the "Additional Pharmacological Characterization", several of the suggested BM mediated mechanisms appears plausible as potential explanations of the observed undesirable effects. However, due to the far upstream position of the transcriptional Keap1/Nrf2 regulatory pathway for many important physiological processes and taking into account that the BM effect may vary depending on tissues and presence or absence of ongoing pathophysiological processes, it appears extraordinary complex to predict the relevance of isolated results from various experimental models. Nevertheless, overall it is concluded the applicant has showed that several of the observed potential adverse effects can be driven by the pharmacological effect by BM on Nrf2 activation instead of by general toxicity.

Pharmacology - Safety pharmacology

An in-vitro hERG test in HEK293 cells gave a potassium channel inhibition estimate of ~9.5% at 0.15uM bardoxolone methyl. The applicant states that this is a 750x margin to the clinical un-bound bardoxolone methyl fraction. It is unclear how this margin was calculated. A clinical mean AUC value of 263 ngxh/mL was used by the applicant as representative for systemic exposure in humans. The corresponding mean C_{max} is 18.7ng/mL. With an Mw of 505.7g/mol and a human plasma protein binding of 94.4%, this gives an C_{max}-dependent total concentration of 0.037uM and a free unbound concentration of ~0.0021uM. This in turn gives a margin of around 71.4x.

A number of cardiovascular parameters (reduced systolic, diastolic, and mean arterial pressures, reduced heart rate, weak to moderate increase in RR and PR-intervals, increase in QT-intervals, and decrease in cQT-intervals) were altered at all doses (5, 60 and 120mg/kg) in the safety pharmacology study in cynomolgus. It can be noted that there was a trend of reduced blood pressure in the clinical data. The applicant argues that these effects were not adverse because of their transient nature and within / only a slight difference from historical control data and in some cases not following a monotonic dose-response. Non-monotonic dose-responses may be an aspect of that there were relatively few animals in the experimental group(s) and/or that some animals vomited after oral

exposure, influencing systemic exposure levels. While the effects were transient and there was no mortality or severe health problems among the animals, these were clear physiological changes in endpoints that are the purpose of safety pharmacology testing. Furthermore, considering the consistent and sometimes marked changes compared to controls across *nearly all* cardiovascular parameters measured (even if mostly near or within historical control range) plus alterations in body temperature (reduction of ~0.5C), the CHMP does not agree with a high dose NOAEL (120mg/kg) but considers these signs adverse from the lowest dose (NOAEL <5mg/kg).

The applicant also argues that there are no systematic or substantial changes in pulmonary function, but the presented data gives a clear pulmonary LOAEL at 120mg/kg (possible NOAEL at 60mg/kg). While the effects in the study cannot be ignored, the more long-term exposure relevance of these findings is unclear. In the toxicology section, in cynomolgus studies up to one year duration (although not focused on cardiovascular-physiological endpoints), there were no mortality or severe health issues. There were also no clear clinical trial signs of cardiovascular problems. While this suggests a certain degree of cardiovascular safety in primates even after longer exposures, it does not fully remove the uncertainty of the findings (especially in a context of no exposure margins and where patients may take the medication over several years and possibly age into becoming a cardiovascular-sensitive population).

In conclusion, the applicant is requested to describe the cardiovascular and pulmonary findings in the SmPC 5.3 (e.g., reflecting NOAEL/LOAEL) but in manner that also provides a context from the more long-term cynomolgus toxicity studies.

Pharmacokinetics - Metabolism

There is a substantial uncertainty with the proposed metabolic profile derived from radiolabeled in-vivo studies (cynomolgus and human) as the position of the ^{14}C-radiolabel is located in a metabolically unstable position in bardoxolone methyl (at the C2-position on the A-ring). This position was used in both metabolism and mass balance studies. As such, there may exist several metabolites where the C2-group has been removed and the reported proportions of the various metabolites to each other may also be misleading. The same problem affects both the non-clinical and human pharmacokinetics dossiers, and it is the basis for a cross-disciplinary Major objection (MO) (for more details, see pharmacokinetics section, and see also LoQ).

Besides the radiolabel-issue, there are several other aspects of the metabolism experimental program that could have been developed further. In the in-vitro assessment, only microsomes and supersomes were used. No hepatocyte studies were included despite the clinical (and toxicological) signs of hepatobiliary effects. The process of generation of the presently predominant M30 metabolite (e.g., biochemical process, enzymes) also remains unclear. The applicant claims that the C17-metabolites are the main agent in rodent toxicity and that these metabolites are rodent specific. Rat CYP2C6 has experimentally been identified as the relevant enzyme for generating these metabolites. Based on microsome studies and that the CYP2C6 gene has no clear homologue in primates, it is claimed that C17-metabolites are only generated in rodents (and minipig), but no experiments similar to the CYP2C6 experiment have been conducted with human (or cynomolgus) CYPs. Long-term toxicity studies in cynomolgus did not use sodium sulphite to protect TK-samples, so no information can be derived from those studies. That being said, as the radiolabel remains in the C17-metabolites, it would be expected that a greater presence should have been detected in the PK-cynomolgus study if these metabolites are a major presence in cynomolgus. A non-clinical concern about the C17-metabolites is the nature of the evidence underlying the applicants claim that they are responsible for all or some of the observed rodent (and minipig) toxicity (see toxicological discussion).

Regarding the listed but unidentified metabolites ('putative hydroxylated metabolites': A, C, D_2, E_1, E_2 and E_3), various combinations of these metabolites have been investigated and/or detected in the

plasma (although at different proportions/extent) in human plasma and animal models. All species have a relatively similar putative hydroxylated metabolite profile (with the possible exception of minipig which seems to have fewer of these metabolites than human, cynomolgus, rat, mouse, hamster, and dog). The absence of identification of these metabolites is an additional dossier weakness in the overall metabolite identification program. A noteworthy difference between species is the absence of the A-metabolite in primates and minipig. Although an uncertainty, as only C17-metabolites have been claimed to be responsible for toxicity (especially in rodents), this has not been made a subject for questioning.

Toxicology

A full program of toxicology studies has characterized the toxicity of RTA 402 and the pivotal studies were performed in accordance with GLP regulations. Studies were conducted in mice, rats, hamsters, dogs, minipigs and monkeys. Multiple toxicological findings were reported, and some findings recured in several species but with different severity while other findings showed a more species-specific pattern.

Treatment related mortalities occurred in hamsters, mice, rats, dogs and monkeys but had different causes for different species. The rodents all showed severe toxicity affecting multiple organs and numerous animals were found dead, euthanized in extremis, or terminated early. In beagle dogs, the original study plan was reduced from 39 weeks to 26 weeks due to significant toxicity. In addition, doses were lowered and several animals in the top two dose levels had sporadic drug holidays due to tolerability issues. Despite these adjustments, several animals were euthanized in extremis. The cause of moribundity for the animals dying or euthanized in extremis was primarily attributed to GI findings; however, other bardoxolone methyl-related findings most likely contributed to an overall poor health of these animals. The monkeys did not show the same toxicity as either rodents or dog. Nine monkeys were sacrificed in extremis during the study and the causes were gavage error or dosing error. No mortalities occurred in the minipig.

Clinical signs were most pronounced in rodents and dogs. Rodents showed a plethora of clinical signs, while in the dogs, the GI-tract was most affected. Most notable clinical signs in the monkeys were soft and/or watery feces. According to the applicant, these clinical signs can partly be explained by the sesame oil vehicle, however, it is not clear what evidence this is based on. Sesame oil is not used in the clinical setting. The minipigs showed no treatment-related clinical signs, no statistically significant effects on body weight, and food consumption was unaltered in the treatment groups.

Effects on haematology parameters were most pronounced in rats and dogs. After the 4-week recovery period in rats, most parameters (but not all) had returned to levels similar to controls. In monkeys, only minor differences not considered to be toxicologically relevant were observed in the 12-month study and no alterations were seen at the recovery interval of analysis. In the minipig, statistically significant changes in haematology parameters were observed but these changes were considered mild and not accompanied by clinical consequences.

Alterations in clinical chemistry was most severe in rodents and dogs. In the mice, changes in clinical chemistry corresponded to microscopic findings in the liver (hepatocellular degeneration/necrosis, single cell necrosis and/or centrilobular to panlobular hypertrophy). Also, in mice euthanized early, changes in clinical chemistry indicate renal effect and corresponded to the microscopic findings of pelvic dilation, necrosis, tubular degeneration/regeneration, casts, haemorrhage, fibrosis, and/or mineralization in the kidney. Several clinical chemistry parameters were altered in rats but most of them recovered during the 4-week recovery period. In dogs, numerous test article-related alterations were observed. Alterations in clinical chemistry parameters in monkeys and minipigs were mild and for the most part reversible.

RTA 402-related alternations in urine parameters were few or absent across all species tested.

Organ weights was most effected in rodents and dogs. Some organ weight changes were noted in monkey and minipigs but either partial recovery was seen, or they were considered to be most likely incidental.

Macroscopic findings in rodents involved a number of different organs. Macroscopic findings in dogs involved several parts of the GI tract but also a few other organs such as thymus, pancreas and mesenteric lymph node. In monkeys, a few animals presented with small thymus a few with body fat depletion. In addition, the monkeys had multiple macroscopic findings associated with gavage error. In minipigs, pale kidneys were reported in two animals.

Following the same pattern as previous parameters, microscopic findings were most severe in rodents and dogs and affected multiple organs. In the monkey, several microscopic findings were considered to be secondary to aspiration, gavage error, and/or gavage related trauma and were not considered to be test article related. However, test article-related findings were present in the gallbladder, liver and thymus at day 186 and 354; at the end of the 4-week recovery period, test article-related microscopic finding were present in the liver of one male at 100/30 mg/kg/day and one male at 300 mg/kg/day, consisting of minimal bile duct hyperplasia. In minipigs, changes were observed in the GI-tract. Full recovery was seen in the tongue, oesophagus, non-glandular stomach, jejunum and ileum. Partial recovery was observed in the duodenum. In general, microscopic changes in the monkey and minipig were in mild and did not involve all animals. However, treatment related effects on indicated organs cannot be excluded.

Findings in the kidneys are of special concern given the proposed indication and patient population. Strikingly, 27/28 mice that were euthanized or found dead prior to scheduled necropsy in the 26-week study had gross necropsy findings in the kidney including: kidney cysts or enlarged kidneys, pelvic dilation, necrosis tubular degeneration/regeneration, casts, and/or haemorrhage in males and females at both dose levels. In addition, kidneys were affected in the minipig with changes present in all treatment groups. Increased kidney weight, although only statistically significant in males, was observed. A moderate diffuse proliferative glomerulonephritis was observed in one male. A similar glomerular change was reported in three other animals, however, described as minimal/slight, multifocal/diffuse, segmental glomerulonephritis. Urine volume was increased, creatinine was decreased in all dose groups for females with similar trend in males. A treatment effect cannot be excluded. In the monkey, occasional kidney findings were reported. The applicant is invited to discuss the kidney findings in the non-clinical studies, their relevance for patients and update SmPC accordingly**.**

GI-tract findings were reported from all species. Mice, rats, hamsters, and monkeys were administered sesame oil (vehicle) or RTA 402 as a suspension in sesame oil. Emesis and soft or watery faeces were observed in most groups, and according to the applicant, these clinical findings could partially be attributed to the sesame oil, but the applicant has not explained how the sesame oil would cause these clinical findings. Importantly, there are finding supporting that RTA 402 itself causes GI toxicity. In the 28-day study in monkeys, soft and/or watery faeces was noted with greater incidence in the treated group. In the oral embryo-foetal and postnatal development study in monkeys (RTA402-P-1101), the animals did not receive sesame oil, but all test item-treated groups showed liquid or soft faeces. The number of affected animals and the intensity of the signs of diarrhoea showed a clear dose-relationship. Minipigs and dogs did not receive the sesame oil in the repeat dose studies. In minipigs, minimal-slight changes were reported in the tongue, oesophagus and non-glandular stomach and was characterized as an increased thickness of the squamous epithelium, involving mainly middle to outer portions. Elongation of villi was present in the small intestines. The dog displayed extensive GI-toxicity with microscopic findings in stomach (cardia, fundus, and pylorus), small intestine (duodenum,

jejunum, and ileum) and large intestine (cecum, colon, and rectum). The GI tract is of particular concern given the AEs reported in the clinical trials. The applicant is asked to discuss the non-clinical GI tracts findings and update the SmPC accordingly.

Adverse findings in spleen and thymus accompanied by test article-related changes in peripheral blood leukocyte analysis was seen in the 12-month repeated oral dose study in cynomolgus monkeys. Corresponding findings were also seen in other animals. In section 4.6 of the NC Overview (Immunotoxicity) referring to the 1-year monkey study the applicant has stated: "No adverse bardoxolone methyl-related changes were reported for T cells (mature, CD4+, and CD8+) and natural killer (NK) cells in males or females". However, this disagrees with the conclusion in the actual study report ("Test article-related increases were noted in the relative percentage and absolute counts of monocytes and B lymphocytes in the 100/30 and 300 mg/kg/day dose levels in males and females. Females exhibited decreases in the relative percentage of mature T cells and CD4+ T cells at 6 and 12 months. Males at all dose levels did not show significant changes in relative percentages and absolute cell counts of CD4+ T cells and CD8+ T cells at 6 and 12 months but did show significant decreases in the percentage of mature T cells at 6 and 12 months"). The applicant is asked to discuss a possible immunosuppressive effect of bardoxolone methyl.

Regarding studies in rodents, oral administration once daily of RTA 402 to mice, rats and hamsters caused significant toxicity and mortality at exposures of RTA 402 even lower than clinical exposure. The applicant claims that the toxicity is caused by a rodent-specific metabolism of RTA 402 producing the C17-carboxylic metabolite RTA 401 and that rodents, therefore, are not useful models for predicting human toxicity. However, the mechanism of toxicity for RTA 401 has not been established and it is not clear if all or only some of the adverse changes observed in rodents were caused by RTA 401, or if some, in fact, were caused by RTA 402. No in-vivo studies with these metabolites have been submitted and hence, the cause of the toxicity in rodents have not been established. The applicant is asked to clearly summarize all evidence available that supports the claim that C17-carboxylic metabolite RTA 401 is responsible for the excessive toxicity seen in rodents and motivate why no data from rodent studies are included in SmPC.

Regarding the toxicity in dogs, it was pointed out in previous scientific advice that an understanding of the underlying mechanism would be of value. The applicant has provided the following statement: "*The precise mechanism for the observed severe gastrointestinal toxicity in dogs is not completely understood; however, it may be related to an intrinsic sensitivity of dogs to anti-inflammatory agents, species-specific gut irritation from bardoxolone methyl itself, or other unidentified factors*". Further, the applicant claims that the GI toxicity seen in dogs is distinct from, and does not appear to be predictive of, nausea and decreased appetite observed in clinical trials with bardoxolone methyl. In summary, the mechanisms behind the toxicity observed in dogs have not been explained and it is not agreed that all toxicity seen in dogs (GI or other organs) should be disregarded. The applicant is asked to further substantiate the statement that GI toxicity in dogs is not a predictor of human toxicity and motivate why no findings from any organs have been included in the SmPC.

Genotoxicity

The proposed SmPC 5.3 states that Bardoxolone methyl is not mutagenic or clastogenic in the *in vitro* and *in vivo* assays. This is currently not supported since Bardoxolone methyl was considered clastogenic in CHO cells, but not in HPBLs.

The two assays used two different solvents for bardoxolone methyl, DMSO and acetone respectively. This resulted in a lower max concentration of Bardoxolone methyl used in the HPBLs assay compared to the CHO cell assay (0,1ug/mL and 10ug/mL, respectively) due to precipitation problems in the HPBL assay. Given the lower concentration used in HPBLs, the negative results are not considered to negate the clastogenic signal observed in the CHO assay. While the *in vivo* study was negative, it should be

noted that the *in vivo* study was an micronuclei test and not a chromosome aberration test introducing additional uncertainty the overall assessment. The SmPC 5.3. section should reflect that the in-vitro test is positive**.**

Carcinogenicity

The carcinogenic potential of bardoxolone methyl has not been studied in animals. The applicant has provided a carcinogenicity risk assessment based on a weight of evidence approach. Given the apparent dual role of Nrf2 in cancer, the applicant is asked to consider to include malignancy as a potential risk in the RMP. The applicant is invited to further discuss this**.**

Reproductive and developmental toxicity

It is agreed that the rat does not appear suitable for reproductive and developmental toxicity assessment due to severe toxicity following bardoxolone methyl treatment.

The applicants claim that rabbit would be irrelevant is only based on that microsomes from rabbit form several metabolites derived from the hydrolysis of the methyl ester moiety at the C17 position, and not based on any data showing poor tolerability of bardoxolone methyl in rabbits.

The monkeys used in the 12-month repeated-dose study were juvenile, corresponding to human ages ranging from approximately 5 to 12 years old. Since adverse effects on reproduction organs only should be determined in animals that have reached sexual maturity, the evaluation of the reproduction organs from the 12-month repeated-dose toxicity study in monkeys is considered of limited value. The applicant is therefore asked to remove information in the SmPC and RMP which refers to the data on reproduction organs from the 12-month repeated-dose toxicity study in monkeys (Study RTA402-P-0709), unless otherwise justified.

While it is also noted that the dogs (which do not form the toxic metabolites) experienced dose limiting GI toxicity, it is not clear why the degenerative changes observed in dog testes (mild bilateral degeneration/atrophy of seminiferous tubules minimal to mild bilateral hypospermatogenesis) and epididymides (bilateral oligospermia/germ cell debris) should be considered secondary to the GI effects and not treatment related. While noted that peripubertal dogs were used (from 5 months of age) and that hypospermatogenesis and atrophy in seminiferous tubules are usually more common in young dogs than in older dogs it is also clear that bardoxolone methyl distributed to reproduction organs in monkeys and rats and that the testis findings in dogs showed a clear increase in incidence and severity compared to the control animals. Therefore, unless, a clear justification can be provided, the testes and epididymides effects observed in the dog 9-month repeat dose toxicity study should be included in the SmPC and RMP**.**

A GLP dose-range finding EFD study was conducted in Göttingen minipigs. Although the minipig appears to form low levels of the toxic C17 metabolites, bardoxolone methyl was well tolerated and the applicant considers the minipig to be a relevant species. It is also noted that the minipig was used in the pivotal repeated-dose toxicity studies without any indications of severe toxicity. That given, it is not clear why the applicant did not choose to perform a definitive EFD study in minipigs but instead choose to perform an ePPND study in monkeys. Studies in monkeys are usually not encouraged and monkeys should only be used when it is considered to be the only relevant species.

There were effects on reproduction parameters and malformations in the minipig study. According to the applicant, incidental inhalation of bardoxolone methyl due to the capsule dosing procedure confounded the results. While it is agreed that there seems to have been dosing issues, the study did result in systemic exposure and mis-dosing is not considered to be able to explain the observed post-implantation loss and malformations. Moreover, it is noted that effects were seen in animals without

any clinical signs indicating that they are related to treatment. The findings should be reflected in the SmPC unless a clear justification for not including them can be provided**.**

The applicant also argues that the foetal effects are not related to treatment since the incidences were within the historical controls of the laboratory. This is not agreed, and the findings appear to be treatment-related. Unless a clear justification can be provided, the applicant is asked to include the minipig foetal findings in the SmPC**.**

No formal juvenile toxicity study has been performed, although bardoxolone methyl is planned to be given to adolescents from 12 years of age. Considering the toxic C17-carboxylic acid metabolites formed in rodents and resulting in severe toxicity, the lack of rodent juvenile studies is acceptable. Moreover, the age range of monkeys dosed with bardoxolone methyl in the 12-month GLP toxicity study corresponds developmentally with humans in the age range of 5 to 12 years old. The need for a juvenile toxicity study was discussed in an CHMP scientific advice EMA/CHMP/SAWP/599796/2018) which concluded that no juvenile toxicity study would be needed provided no specific concerns were raised following completion of the reproduction studies in the monkey. It can be noted that recently published literature on the role of Nrf2 in bone metabolism suggests that Nrf2 can mediate disturbances of normal bone homeostasis, which would be especially important in growing children. In the ePPND study in monkeys, mild decreases in ossification were observed for some parameters. However, the effects appeared to more sporadic and possibly linked to decreased foetal body weight/growth and hence they are not considered strong enough to warrant further justification.

Other toxicity studies

Mechanistic in vitro studies with metabolites

While it is acknowledged that the applicant considers the *in vitro* hepatocyte experiments supportive of that the C17-carboxylic acid metabolite RTA 401 induces cholestasis in rat hepatocytes, but not human or monkey hepatocytes, the data are considered of limited value in explaining the severe toxicities affecting multiple organ systems in rodents.

applicant is invited to present the Report on determination of MEC since there is only the result presented.

Environmental risk assessment

Based on a refined Phase I PECsw < 0.01ug/L, no Phase II Risk assessment is necessary. Yet bardoxolone methyl has also a log Kow value of >5.17 (i.e., log Kow > 4.5), and the applicant has not conducted any Phase II PBT assessment. This is not acceptable and a commitment for an PBT assessment is requested (a stepwise procedure starting with persistence, followed by bioaccumulation and finally, if needed, aquatic toxicity is recommended). As a result of the absence of an PBT assessment, the available data do not allow to conclude definitively on the potential risk of bardoxolone methyl to the environment.

3.2.7. Conclusion on non-clinical aspects

Overall, there is a cross-disciplinary major objection concerning metabolite characterization in human and non-clinical animal models (MO, Non-clinical kinetics and human kinetics) that needs to be resolved. Besides the MO, there are a number of pharmacological, toxicological and ecotoxicological OCs that also require responses from the applicant (some influencing the wording in the SmPC).

3.3. Clinical aspects

Tabular overview of clinical studies

Table 1. Bardoxolone methyl biopharmaceutic and clinical pharmacology studies.

Study Number/Phase	Type of Study	Number of Subjects/Patients	Dose Form(s) Studied	Duration of Treatment
402-C-0901/ Phase 1	Biopharmaceutic	19 Bard	150 mg crystalline 30 mg amorphous SDD	Single dose each formulation
402-C-1901 Phase 1	Comparative BA	74 Bard	5, 10, 15, 30 mg amorphous SDD	Single dose each formulation
402-C-1003 Phase 1	ADME	6 Bard	20 mg [^{14}C]-labeled amorphous SDD	Single dose
402-C-1002 Phase 1	Hepatic impairment	34 Bard	20 mg amorphous SDD	Single dose
402-C-0501 Phase 1	Dose escalation in patients with advanced solid tumors or lymphoid malignancies	47 Bard	5, 10, 20, 40, 80, 150, 300, 600, 900, 1300 mg crystalline	21 days
402-C-1004 Phase 1	Food effect/Dose proportionality	32 Bard	20, 60, 80 mg amorphous SDD	Single dose
402-C-1104 Phase 1	DDI; digoxin, rosuvastatin	32 Bard	20, 60 mg amorphous SDD	5 days
402-C-1105 Phase 1	DDI; midazolam, repaglinide	40 Bard	60 mg amorphous SDD	Single dose
402-C-1701 Phase 1	DDI; itraconazole	16 Bard	10 mg amorphous SDD	Single dose
402-C-1006; 402-C-1006 Supplementary Report Phase 1	TQT	89 Bard 45 Placebo	20, 80 mg amorphous SDD	6 days
402-C-1102 Phase 2	PK/PD in patients with T2D CKD	24 Bard	20 mg amorphous SDD	8 weeks
Total Patients		413 Bardoxolone methyl 90 Placebo		

Abbreviations: ADME=absorption, distribution, metabolism, and excretion; BA=bioavailability; CKD=chronic kidney disease; DDI=drug-drug interaction; PD=pharmacodynamic; PK=pharmacokinetic; SDD=spray-dried dispersion; T2D=type 2 diabetes; TQT=Thorough QT

Table 2. Bardoxolone methyl clinical studies in patients with Alport syndrome.

Study Number **Study Abbreviation[a]/Name** **NCT#** **EudraCT#**	**Study Design (Duration)** **Status** **Data Cutoff**	**Location (s)**	**Dose Level** **Formulation**	**Number Patients Enrolled** **Adults ≥18 years old** **Pediatrics <18 years old**
402-C-1603 Study 1603 Phase 3[b]/ CARDINAL Phase 3 NCT03019185 EudraCT 2016-004395-22	Randomized, double-blind, placebo-controlled, parallel-group (2 years) Completed 06 Nov 2020	US, EU (France, Germany, Spain), UK, Japan, Australia	5-20 mg or 5-30 mg Amorphous SDD	157 66 Bard/68 placebo 11 Bard/12 placebo
402-C-1603 Study 1603 Phase 2/ CARDINAL Phase 2 NCT03019185 EudraCT 2016-004395-22	Open-label (2 years) Completed 04 Oct 2019	US	5-20 mg or 5-30 mg Amorphous SDD	30 Bard 28 Bard 2 Bard
402-C-1803 Study 1803/EAGLE[c] NCT03749447 EudraCT 2018-003253-24	Open-label (safety extension of 402-C-1603) Ongoing 18 Jan 2021 (interim database lock)	US, Japan, Australia	5-20 mg or 5-30 mg Amorphous SDD	96 Bard (enrollment ongoing) 88 Bard 8 Bard

Abbreviations: Bard=bardoxolone methyl; EudraCT=European Union Drug Regulating Authorities Clinical Trials Database; NCT=National Clinical Trial; SDD=spray-dried dispersion.

[a] Designation used for the study in this Clinical Overview.

[b] Study 1603 Phase 3 provides the primary efficacy and safety data to support this application.

[c] Note that the number of patients enrolled in Study 1803 is a subset of the patients enrolled in Study 1603 Phase 2 and Study 1603 Phase 3.

Table 3. Supportive studies in Non-Alport Syndrome indication

Indication Study Number	Study Phase	Dose Form(s) Studied	Number of Patients
Hepatic Dysfunction 402-C-0701	1/2	5, 25, 50 mg crystalline	12 Bard, 4 Placebo
Type 2 Diabetes CKD 402-C-0903 (BEACON)	3	20 mg amorphous SDD	1088 Bard; 1097 Placebo
RTA402-005 (TSUBAKI)	2	5 to 15 mg amorphous SDD	65 Bard; 55 Placebo
402-C-0804 (BEAM)	2b	25, 75, 150 mg crystalline	170 Bard; 57 Placebo
402-C-0902	2	2.5, 5, 10, 15, 30 mg amorphous SDD	131 Bard
402-C-1005	1	20 mg amorphous SDD	12 Bard, 6 Placebo
Diabetic Nephropathy 402-C-0801 (Stratum 1)	2a	25, 75, 150 mg crystalline	60 Bard
402-C-0801 (Stratum 2)	2a	25 to 75 mg crystalline	20 Bard
Rare CKD[a] 402-C-1702 (PHOENIX)	2	5 mg to 30 mg amorphous SDD	103 Bard
Pulmonary Hypertension[b] 402-C-1602 (RANGER)[c]	3a	10 mg amorphous SDD	261[d] Bard
402-C-1302 (LARIAT)	2	2.5, 5, 10, 20 mg amorphous SDD	Part 1: 115 Bard, 51 placebo Part 2: 137 Bard
Pancreatic Cancer 402-C-0702	1/2	150, 200, 250 mg crystalline	34 Bard
		Total Patients	2004 Bardoxolone methyl 1270 placebo

Abbreviations: ADPKD= Autosomal dominant polycystic kidney disease; Bard=bardoxolone methyl; CKD=chronic kidney disease; FSGS=focal segmental glomerulosclerosis; IgAN=immunoglobulin A nephropathy; SDD=spray-dried dispersion; T1D=type 1 diabetes.

[a] IgAN, FSGS, T1D, and ADPKD

[b] Patients in LARIAT Part 1 were eligible to enroll in LARIAT Part 2, and all patients in LARIAT were eligible to enroll in RANGER

[c] Study ongoing as of the cutoff date (20 February 2020). The study has since been terminated and the CSR is in progress.

[d] As of the data cutoff date (20 February 2020), one patient did not receive treatment. Therefore, a total of 258 patients have received at least 1 dose of bardoxolone methyl in this study

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

The pharmacokinetic data has been retrieved from studies summarised in Table 1, Table 2 and Table 3.

A population PK analysis and PBPK model is provided.

An *in vitro* package characterizing *in vitro* metabolism, protein binding, whether bardoxolone methyl is a substrate of metabolizing enzymes or transporters as well as potential to inhibit or induce enzymes or transporters is also provided.

A marketing authorization is sought for bardoxolone methyl capsules (5 mg and 15 mg) with dose titration over a dose range of 5 mg to 30 mg. The maximum recommended daily dose for the treatment of CKD caused by Alport syndrome is 20 mg or 30 mg depending on the UACR pre-treatment level (higher dose for UACR >300 mg/g). Most of the clinical pharmacology studies were done with 20 mg capsule which is not intended for the market.

Methods

Bioanalysis

Plasma concentrations of bardoxolone methyl were analysed with LC-MS/MS methods. Sodium sulfite was added to plasma samples to prevent ex vivo oxidative degradation of bardoxolone methyl.

Non-compartment data analysis

Standard non-compartmental analysis was performed in all studies where rich sampling was applied.

Population PK analysis

A PopPK model was developed for bardoxolone methyl using rich and sparse PK data from 8 clinical studies of bardoxolone methyl (Studies 0903, 1002, 1004, 1006, 1102, 1302, 1603 Phase 2, 1603 Phase 3 Year 1, and 1702) in healthy subjects and patients with Alport syndrome, PAH, T2DM CKD, and other rare CKDs. The PK of bardoxolone methyl was described by a 2-compartment model with first-order absorption, lag time, and linear clearance. Race (black vs non-black), disease population (reference: Alport syndrome/T2DM CKD/PAH vs Disease Population 2: healthy/T1DM CKD/ ADPKD/FSGS/IgAN/hepatic impairment), and renal function (time-varying eGFR) had significant effects on bardoxolone methyl PK parameters and were included in the model. The final PopPK model parameters are presented in Table 4. Prediction-corrected visual predictive check (pcVPC) plots are shown in Figure 1.

Table 4. Final Model Parameter Estimates for Bardoxolone Methyl PK

Parameter (unit)	Estimate		Sampling Importance Resampling		Shrinkage (%)
	95% CI	RSE (%)	95% CI	RSE (%)	
K_a (1/h)	0.660 [0.59, 0.73]	5.41	0.594, 0.736	5.49	-
CL/F (L/h)	171 [165, 178]	1.99	165, 178	2.02	-
V_c/F (L)	2330 [2050, 2610]	6.17	2140, 2540	4.48	-
V_p/F (L)	11800 [9260, 14300]	11.0	10400, 13500	6.90	-
Q/F (L/h)	98.3 [86.5, 110]	6.13	91.4, 106	3.89	-
Absorption lag time (h)	0.484 [0.477, 0.49]	0.663	0.478, 0.489	0.606	-
Black race effect on CL/F	0.462 [0.341, 0.584]	13.4	0.331, 0.584	13.7	-
Disease Population 2 effect on K_a	1.08 [0.726, 1.42]	16.6	0.718, 1.37	15.9	-
Time-varying eGFR effect on V_c/F [a]	-0.492 [-0.627, -0.357]	14.0	-0.596, -0.395	11.0	-
Disease Population 2 effect on V_c/F	1.70 [1.46, 1.94]	7.27	1.43, 1.97	8.14	-
Black race effect on V_c/F	0.529 [0.363, 0.696]	16.1	0.365, 0.7	16.4	-
Interindividual variability (IIV)					
IIV on K_a	2.40 [1.83, 2.97]	12.1	2.00, 2.94	10.3	48.1
K_a ~ CL/F	0.238 [0.133, 0.343]	22.5	0.147, 0.333	19.5	-
IIV on CL/F	0.350 [0.31, 0.39]	5.82	0.316, 0.387	5.07	15.6
K_a ~ V_c/F	0.307 [0.144, 0.47]	27.1	0.189, 0.446	21.7	-
CL/F ~ V_c/F	0.339 [0.287, 0.391]	7.86	0.301, 0.385	6.26	-
IIV on V_c/F	0.428 [0.34, 0.515]	10.4	0.365, 0.518	8.94	22.7
Random unexplained variability (RUV)					
Additive error (ng/mL)	0.0507 [0.028, 0.0733]	22.8	0.0457, 0.0559	5.17	9.7
Proportion error	0.4300 [0.415, 0.446]	1.87	0.42, 0.44	1.14	

Abbreviations: CI=confidence interval; CKD=chronic kidney disease; CL/F=apparent clearance; eGFR=estimated glomerular filtration rate; K_a=absorption rate constant; Q/F=apparent intercompartmental clearance; RSE=relative standard error; T1DM CKD=CKD associated with type 1 diabetes mellitus; T2DM CKD=CKD associated with type 2 diabetes mellitus; V_c/F=apparent central volume of distribution; V_p/F= apparent peripheral volume of distribution

[a] Covariate effects were incorporated using a power function.

Source: REAT-PMX-BARD-1532, Table 21.

The typical individual is of non-black race with eGFR of 33 mL/min/1.73 m^2 and with T2DM CKD, pulmonary arterial hypertension, or Alport syndrome. Disease Population 2 consists of healthy subjects and patients with T1DM CKD, autosomal dominant polycystic kidney disease, focal segmental glomerulosclerosis, immunoglobulin A nephropathy, or hepatic impairment.

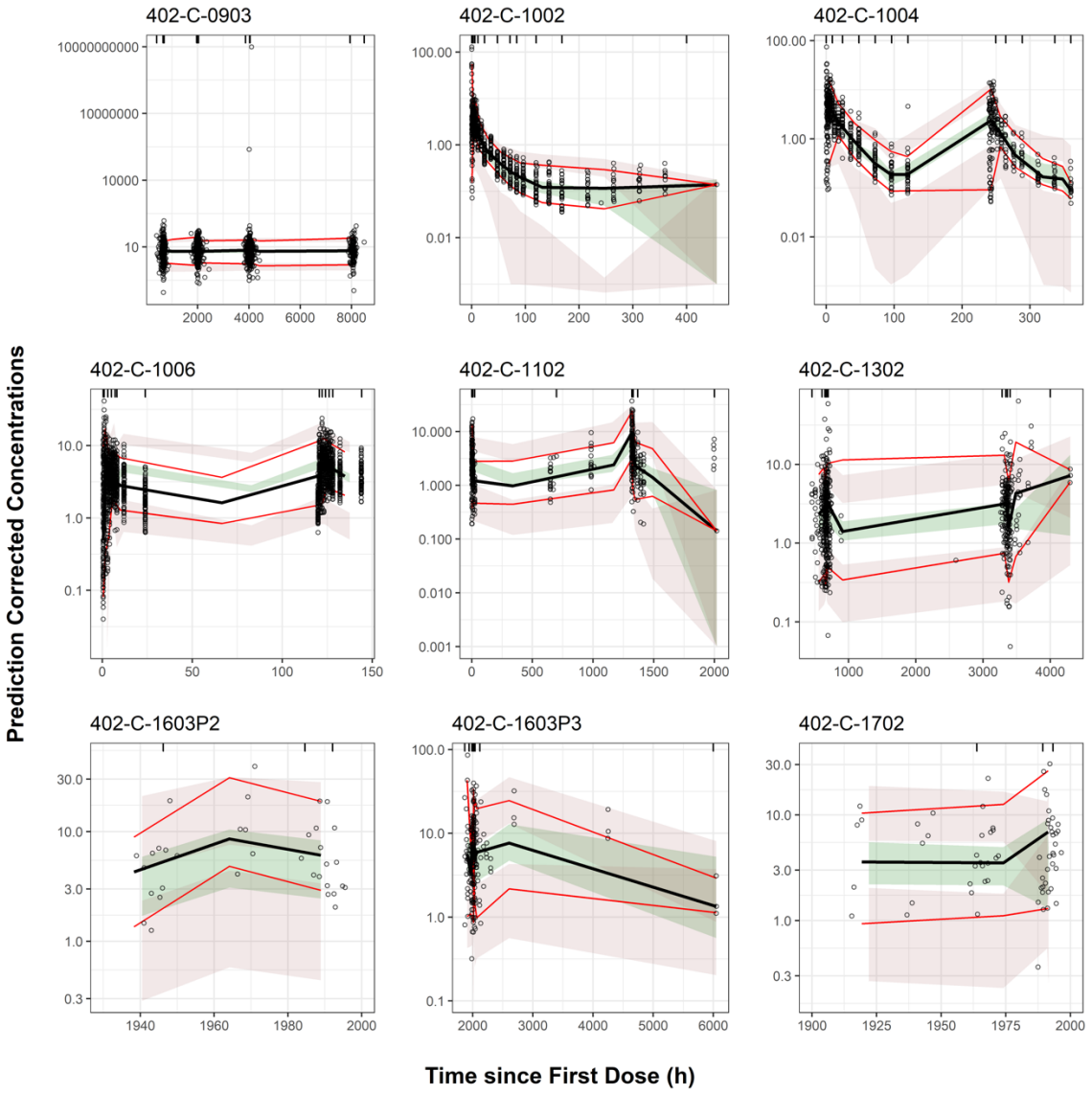


Figure 1. Prediction-Corrected Visual Predictive Check of the Population Pharmacokinetic Model for Bardoxolone Methyl Stratified by Study

Source: REAT-PMX-BARD-1532, Figure 20.

The open circles represent the observed data. The solid black lines represent the median of the observed data, and the solid red lines represent the 5th and 95th percentiles of the observed data. The green-shaded areas represent the 90% CI of the median of the simulated data, and the red-shaded areas represent the 90% CI of the 5th and 95th percentiles of the simulated data.

Physiologically-based pharmacokinetic model-based analysis

A PBPK model for bardoxolone methyl was developed using data from Study 402-C-1003 and verified with data from Studies 402-C-1004 and 402-C-1701 to support evaluation of effects of DDIs (weak, moderate, and strong CYP3A4 inhibitors and moderate and strong CYP3A4 inducers) on bardoxolone methyl PK.

Absorption

Across single dose studies performed during fasting conditions, absorption occurred with median t_{max} 2-5 hours, see Table 5.

Table 5. Summary of Key Bardoxolone Methyl Single-Dose PK Parameters in Healthy Subjects Across Studies. All doses given in the fasted state as spray-dried (SDD) formulation.

Dose Level Study Number	Number of Capsules Delivering Dose	N	Geometric Mean (CV%) [a]					
			C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng*h/mL)	CL/F (L/h)	V_z/F (L)	$t_{1/2}$ (h)
10 mg Bardoxolone Methyl								
402-C-1701	1 capsule	16	2.43 (34.5)	2.50 [2.00, 5.00]	27.8 (46.0)	359.20 (50.3)	9701.6 (31.1)	18.72 (33.4)
402-C-1901	1 capsule	36 [b]	2.85 (43.1)	2.51 [1.00, 6.00]	35.7 (47.8)	307 (41.0) [c]	13043 (44.7) [c]	35.5 (67.6) [c]
402-C-1901	2 capsules	35 [d]	3.10 (49.5)	2.00 [1.00, 6.00]	31.2 (55.2)	362 (51.0) [c]	13789 (41.0) [c]	33.8 (73.2) [c]
20 mg Bardoxolone Methyl								
402-C-1002	1 capsule	17	5.08 (51.3)	3.00 [1.00, 6.00]	89.4 (40.2)	224 (32.2)	18600 (34.3)	57.7 (61.0)
402-C-1003	1 capsule	6	6.25 (32.7)	3.02 [3.00, 4.00]	66.5 (39.1)	322 (36.5)	12327 (45.9)	23.8 (42.3) [e]
402-C-1004	1 capsule	16	5.62 (40.7)	3.08 [1.08, 6.08]	90.5 (45.6)	221 (41.4)	14500 (44.0)	45.6 (32.3)
402-C-1006	1 capsule	45	4.41 (42.3)	4.08 [1.08, 8.08]	NC	NC	NC	NC
30 mg Bardoxolone Methyl								
402-C-1901	1 capsule	35 [d]	3.94 (59.3)	3.00 [1.00, 6.00]	94.4 (49.1)	351 (44.5) [c]	27502 (46.8) [c]	63.2 (49.5) [c]
402-C-1901	2 capsules	36 [f]	8.00 (60.9)	3.00 [1.00, 6.00]	143 (50.7)	232 (44.3) [c]	26903 (49.3) [c]	85.5 (34.8) [c]
60 mg Bardoxolone Methyl								
402-C-1004	3 capsules	8	14.9 (47.0)	2.08 [1.08, 3.08]	280 (55.4)	214 (43.3)	13500 (87.7)	43.7 (51.8)
80 mg Bardoxolone Methyl								
402-C-1004	4 capsules	8	16.5 (28.8)	3.08 [2.08, 6.08]	302 (33.9)	265 (26.3)	15200 (62.5)	39.7 (57.3)
402-C-1006	4 capsules	44	14.0 (56.1)	5.08 [1.08, 8.08]	NC	NC	NC	NC

Abbreviations: $AUC_{0-\infty}$=area under the concentration-time curve from time zero extrapolated to infinity; CL/F=apparent clearance; C_{max}=maximum concentration; CV=coefficient of variation; n=number with estimable parameter; NC=not calculated; PK=pharmacokinetic; $t_{1/2}$=half-life; t_{max}=time to C_{max}; V_z/F=apparent volume of distribution

[a] Median [minimum, maximum] presented for t_{max}.

[b] For $AUC_{0-\infty}$, CL/F, V_z/F, and $t_{1/2}$, n = 34.

[c] Mean (CV%) presented.

[d] For $AUC_{0-\infty}$, CL/F, V_z/F, and $t_{1/2}$, n = 32.

[e] Harmonic mean (CV%) presented for $t_{1/2}$.

[f] For $AUC_{0-\infty}$, CL/F, V_z/F, and $t_{1/2}$, n = 33.

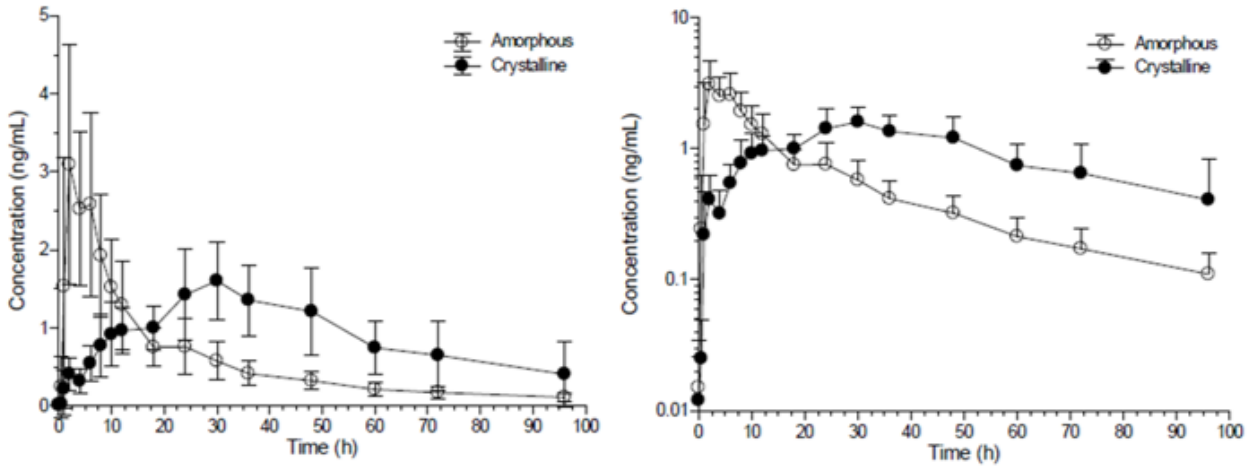
Source: Table 3; Table 6; Table 8; Table 16; Study 402-C-1901 CSR, Table 14.2.2.1; and Study 402-C-1701 CSR, Table 14.2.2.

All doses given in the fasted state as spray-dried dispersion (SDD) formulation bardoxolone methyl capsules.

An absolute human bioavailability study has not been conducted and it is uncertain whether bardoxolone methyl is a high or low permeable compound. Regarding solubility, bardoxolone methyl has low aqueous solubility and is practically insoluble (less than 80 ng/mL) across the physiological pH range (pH 1-pH 7.5). Since high permeability is not demonstrated, the drug substance is considered to have low permeability for BCS classification purposes (according to ICH M9 guideline). Based on this and the poor solubility, bardoxolone methyl is classified as a BCS 4 compound.

To increase the dissolution rate and to enhance the bioavailability, an amorphous form of bardoxolone methyl was developed, which is more soluble than the early capsule formulation using the crystalline form. A spray-dried dispersion (SDD) formulation of the amorphous form of bardoxolone methyl was used in the final formulation to stabilize the amorphous drug substance as a molecular dispersion. The final formulation was used in the clinical studies in patients with Alport syndrome (402-C-1603 and 402-C-1803) and in all clinical pharmacology studies except two studies where the crystalline form was used (402-C-0901; BA-study amorphous vs crystalline and 402-C-0501; dose escalation in patients with solid tumours or lymphoid malignancies), see Table 1 and Table 2.

A single-dose, 2-way crossover, relative bioavailability study was performed with the two formulations of bardoxolone methyl capsule used in clinical development. The pharmacokinetics differ substantially between the amorphous SDD formulation (intended-to-market formulation) and the early crystalline formulation with an earlier t_{max} (2 h vs 30h) and a higher plasma exposure (3-fold higher dose-normalised AUC) for the amorphous SDD formulation, see Figure 2. The PK results in study 402-C-0901 is considered as preliminary since no sodium sulphite was added to the plasma samples.



Left-side panel is in linear scale, and right-side panel is in semilogarithmic scale.
Abbreviations: SD=standard deviation; SDD=spray-dried dispersion

Figure 2. Mean (SD) Bardoxolone Methyl Plasma Concentration-Time Profiles Following Single-Dose Administration of 30 mg SDD Formulation and 150 mg Crystalline Formulation (Study 402-C-0901)

Study 402-C-1901 was conducted to support the potential future commercialization of single-unit capsules (e.g., 10-mg and 30-mg capsules, which are not part of the current application). It was shown that bardoxolone methyl exposures (C_{max} and AUC) were similar when 10 mg was given as a single capsule or as two 5-mg capsules, see Table 5. The 10 mg strength are not applied for but is administered in some of the clinical studies. For the 30 mg strength, bardoxolone methyl exposures (C_{max} and AUC) were significantly lower when 30 mg was given as a single capsule compared to two 15-mg capsules (1-capsule/2-capsule administration GMR 90% CI upper bounds approximately 57% and 74% for C_{max} and AUC, respectively). The 30 mg strength has not been used in any other submitted clinical study in this application.

Administration with a high-fat meal had no effect on the AUC of bardoxolone methyl but the mean C_{max} increased 1.7-fold compared to administration in the fasted state in study 402-C-1004. Median t_{max} occurred at approximately 2 to 3 hours under fasted conditions, compared to approximately 6 hours when administered with a high-fat meal, see Table 6.

Table 6. Summary of Bardoxolone Methyl Pharmacokinetic Parameters Following Fasted- and Fed-State Single-Dose Administration of 20 mg Bardoxolone Methyl (Study 402-C-1004, Part 1)

Treatment Group	n	Geometric Mean (CV%) [a]						
		C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng*h/mL)	$AUC_{0-\infty}$ (ng*h/mL)	CL/F (L/h)	V_z/F (L)	$t_{1/2}$ (h)
Fasted	16	5.62 (40.7)	3.08 [1.08, 6.08]	82.6 (43.4)	90.5 (45.6)	221 (41.4)	14500 (44.0)	45.6 (32.3)
Fed	16 [b]	9.63 (45.3)	6.08 [1.08, 9.15]	80.5 (47.8)	92.1 (49.4)	217 (36.4)	17900 (43.8)	56.9 (32.5)

Note: Last PK sampling timepoint was 120 hours postdose.
Abbreviations: AUC=area under the concentration-time curve; $AUC_{0-\infty}$=AUC from time zero extrapolated to infinity; AUC_{0-t}=AUC from time zero to last quantifiable concentration; CL/F=apparent clearance; C_{max}=maximum concentration; CV=coefficient of variation; n=number with estimable parameter; PK=pharmacokinetic; $t_{1/2}$=half-life; t_{max}=time to maximum concentration; V_z/F=apparent volume of distribution
[a] Median [minimum, maximum] presented for t_{max}.
[b] For $AUC_{0-\infty}$, CL/F, V_z/F, and $t_{1/2}$, n=14.

Distribution

Bardoxolone methyl exhibited an average V_z/F ranging from approximately 9700 to 27500 L in single-dose studies in healthy subjects (Table 5). The estimated V_c/F and V_p/F for a typical non-black patient with Alport syndrome and eGFR of 33 mL/min/1.73 m^2 in the PopPK analysis were 2330 and 11800 L, respectively.

The plasma protein binding determined by ultracentrifugation was 94.4% for bardoxolone methyl and not concentration dependent in the concentration range 10-100 ng/ml. The major binding protein was not determined. The plasma protein binding for M3 (TX64084) and M19 (TX30451) was 98.5% for both the metabolites.

The blood to plasma ratio for bardoxolone methyl was 0.60, suggesting limited penetration into red blood cells.

Metabolism

In vitro

A study was performed in human liver microsomes and recombinant human CYP enzymes to identify the CYP enzymes capable of metabolizing bardoxolone methyl (RTA 402). Substrate disappearance was reported as the sum of bardoxolone methyl and 1,2-dihydro-RTA 402, since bardoxolone methyl is reduced non-enzymatically to 1,2-dihydro-RTA 402. The results indicated that CYP3A4 and CYP3A5 are the major enzymes contributing to the *in vitro* metabolism of bardoxolone methyl. In human liver microsomes, the disappearance of bardoxolone methyl was inhibited up to 77% (Figure 3) by the direct CYP3A4/5 inhibitor ketoconazole. This was confirmed in the *in vivo* DDI study (study 402-C-1701) with a strong CYP3A4 inhibitor (and strong P-gp inhibitor), itraconazole, in which the GMRs for C_{max} and $AUC_{(0-\infty)}$ were 6.9 and 8.7, respectively, when bardoxolone methyl was co-administered with itraconazcole as compared to alone. CYP2C9 seems also to be involved in the metabolism. The disappearance of bardoxolone methyl was inhibited up to 37% by the direct CYP2C9 inhibitor sulfaphenazole (Figure 3).

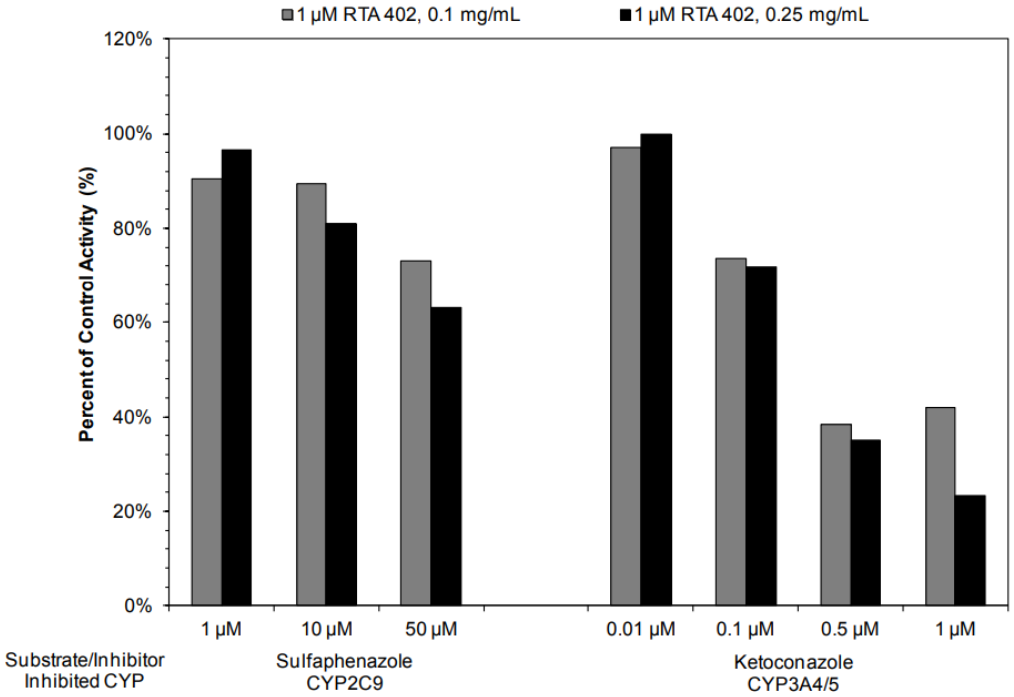


Figure 3. Effect of sulfaphenazole (direct-acting inhibitor of CYP2C9) and ketoconazole (direct-acting inhibitor of CYP3A4/5) on the disappearance of RTA 402 (1 µM) by human liver microsomes (0.1 and 0.25 mg protein/mL)

The applicant has performed *in vitro* metabolism studies in human microsomes using non-labelled bardoxolone methyl. Extensive metabolism was observed with approximately 2%, 4%, and 14% of the parent drug remaining following a 60-minute incubation with 0.5, 1, and 2 µM bardoxolone methyl, respectively. Numerous metabolites were observed but not identified.

In vivo

In the plasma samples for metabolic profiling from the mass balance study, three metabolites were observed in plasma: M30 (76%), M3 (7%) and M19 (8%). Bardoxolone methyl accounted for less than 1% of total radioactivity in plasma. Also in faeces, unchanged bardoxolone methyl accounted for <1% of total radioactivity. The remainder of the dose was excreted as metabolites (M3, M4, M7, M19, M23, M28, M29, M31, M32, U1, and U2), with M3 and M4 as the most abundant metabolites in faeces accounting for 19.8% and 19.8%, respectively. In urine (pooled 288-312 hours), only M30 (thiocyanate) was identified, accounting for 6% of the dose. The proposed metabolites are presented in Figure 4.

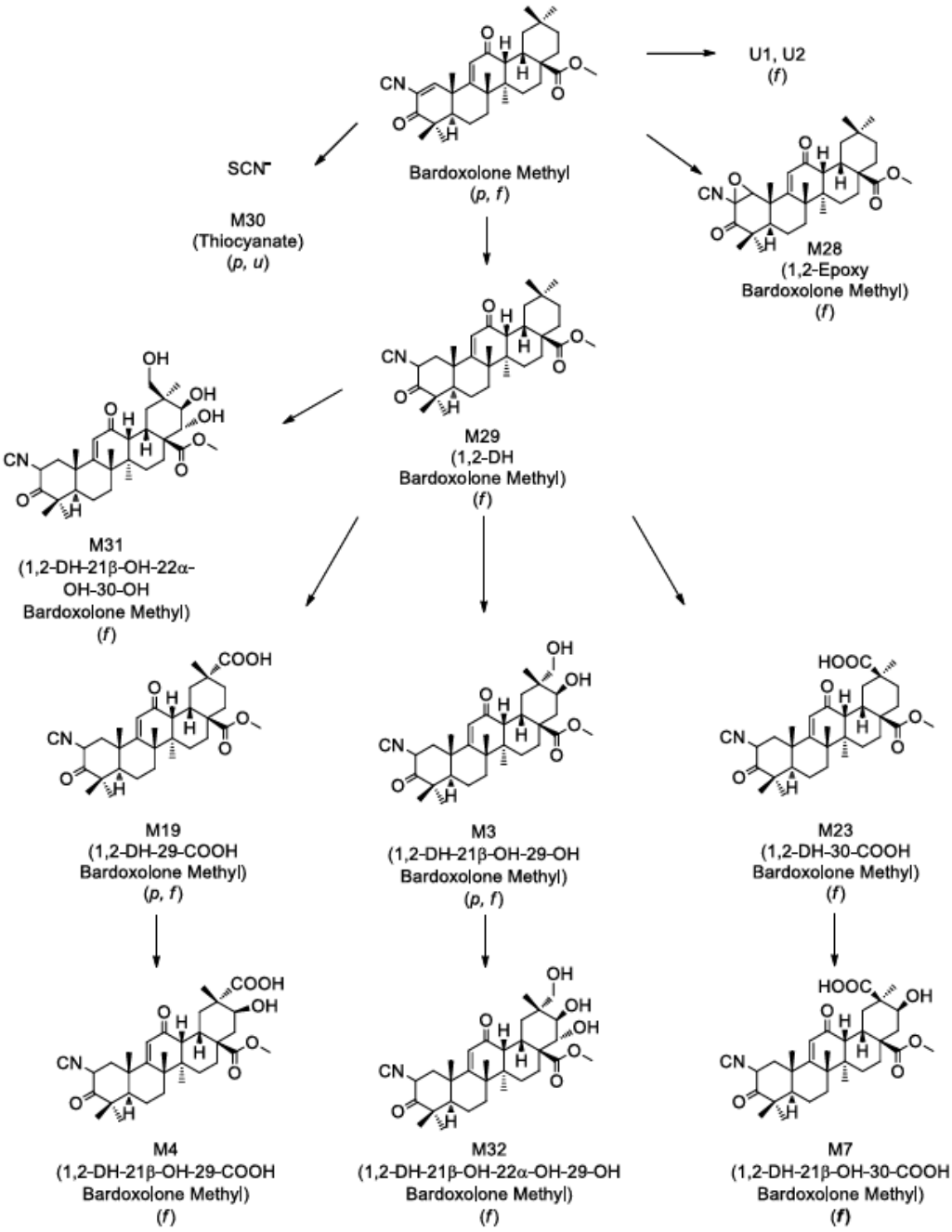


Figure Notes: Metabolites observed in human plasma, feces, and urine are indicated with *p*, *f*, and *u* labels, respectively. The arrows indicate the representative, proposed directions of metabolic cascade for illustration purposes but do not represent chemical reaction.

Figure 4. Proposed Metabolic Pathway for Bardoxolone Methyl in Humans after a Single Oral [14C]Bardoxolone Methyl Administration

The largest metabolite identified in plasma samples from the mass balance study is thiocyanate (76%). In urine, thiocyanate was the only identified metabolite. The 14C-labelling in the nitril-moiety (see Figure 5) is therefore not an adequate position since possible metabolites resulting from the decyano metabolism are "unlabelled" in this study and hence not identified.

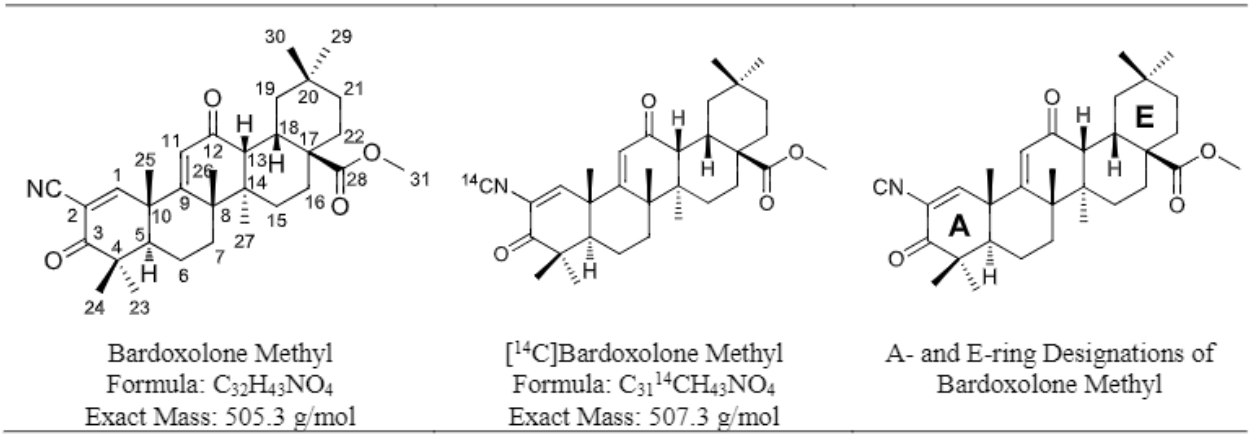


Figure 5. Chemical Structure of Bardoxolone Methyl and [14C]Bardoxolone Methyl

Plasma samples from day 56 in clinical study RTA402-C-0801 were analysed for quantitation of bardoxolone methyl and related metabolites, as previously found in rodent species. No sodium sulphite was added to the plasma samples in study RTA402-C-0801. No carboxylic acid metabolites (C17-metabolites) were be identified in the plasma samples.

Elimination

The plasma half-life of bardoxolone methyl is approximately in the range 19-85 hours (Table 5).

In the mass balance study, the majority (82%) of the radioactivity was excreted in faeces and a smaller part (6%) in urine. Most of the radioactivity in both faeces and urine was in the form of metabolites. In faeces, less than 1% was excreted as unchanged bardoxolone methyl. The mass balance study is however not optimally designed due to the position of the 14C-labelling in the cyanogroup.

Dose proportionality and time dependencies

Indication of dose-proportional increase in plasma exposure was seen, between 20 mg and 60 mg in the single dose study 402-C-1004 and between 20 mg and 80 mg in the multiple-dose study 402-C-1006. The PopPK analysis suggested dose proportionality within the 5 to 80 mg dose range.

The mean accumulation ratio ranged from approximately 1.7 to 3.1 (measured as the ratio of AUC0-24h at steady-state to AUC0-24h after a single dose) following 56 days of dosing of 20 mg bardoxolone methyl once daily in patients with T2DM CKD in study 402-C-1102. Following 6 days of QD dosing (20 mg and 80 mg) in healthy volunteers in study 402-C-1006, the mean accumulation ratio of bardoxolone methyl, based on C_{max} and AUC (AUC0-24) was approximately 1.5.

Pharmacokinetics in target population

The PopPK model was used to generate model-predicted steady-state exposures for patients with Alport syndrome in Studies 1603 Phase 2 and 1603 Phase 3 Year 1 (Table 7).

Table 7 Summary Statistics of Model-Predicted Bardoxolone Methyl Exposures in Patients with Alport Syndrome in Studies 1603 Phase 2 and 1603 Phase 3 Year 1

Exposure Metric	Maximum Dose	N	Mean (SD)	Median (Min, Max)
Study 1603 Phase 2				
Steady-state AUC (ng*hr/mL)	20 mg	20	119 (55.0)	106 (45.8, 274)
	30 mg	9	263 (135)	245 (120, 538)
Steady-state C_{max} (ng/mL)	20 mg	20	10.2 (4.92)	9.84 (2.33, 21.8)
	30 mg	9	18.7 (11.0)	15.7 (6.11, 38.5)
Study 1603 Phase 3 Year 1				
Steady-state AUC (ng*hr/mL)	10 mg	2	64.4 (57.5)	64.4 (23.7, 105)
	20 mg	42	116 (59.3)	96.8 (35.3, 312)
	30 mg	24	223 (155)	174.0 (46.1, 686)
Steady-state C_{max} (ng/mL)	10 mg	2	6.65 (5.72)	6.65 (2.61, 10.7)
	20 mg	42	9.64 (4.19)	8.50 (1.99, 24.7)
	30 mg	24	17.2 (9.22)	15.2 (3.57, 40.2)

Special populations

No dedicated renal impairment study was performed. The applicant refers to the mass balance study where 6% of the radioactive dose was excreted in urine and that patients with various degrees of renal impairment were included in the clinical efficacy studies and renal impairment was evaluated in the popPK analysis. The PopPK analysis dataset included data from studies in the renally impaired population and had a median (range) baseline eGFR of 26.0 (9.00,147) mL/min/1.73 m². Bardoxolone methyl V_c/F was predicted to be higher with lower eGFR (time-varying) in the PopPK analysis. To guide dosing recommendations, simulations using the PopPK model were performed to assess the potential effects of renal function on bardoxolone methyl steady-state exposures. Simulations were conducted at 20 mg QD dosing and used individual posthoc PK parameter estimates for all subjects in the PopPK analysis dataset. Model predictions demonstrate a lack of notable difference between subjects of varying renal impairment relative to subjects with normal renal function (ratio of median exposures within 1.01 to 1.19.

A dedicated hepatic impairment study was conducted and the mean total plasma exposure ($AUC_{0-\infty}$) of bardoxolone methyl following a 20 mg single oral dose was approximately 38%, 84%, and 79% higher in subjects with mild, moderate, and severe hepatic impairment, respectively, as compared with subjects with normal hepatic function. Hepatic impairment did not appear to alter C_{max}. The terminal plasma half-life was prolonged with increased severity of hepatic impairment.

No clinically relevant effects of bardoxolone methyl PK due to gender, race or age are expected. Body weight was neither statistically significant in the popPK analysis.

Interactions

The drug-drug interaction potential of bardoxolone methyl was characterized to assess whether bardoxolone methyl is a substrate, inhibitor and/or inducer of metabolizing enzymes, and a substrate and/or inhibitor of various transporters. Studies were also performed to assess whether the metabolites, M3 and M19, inhibits CYP enzymes and/or transporter proteins.

Bardoxolone methyl as victim

In vitro studies showed that bardoxolone methyl is mainly metabolised by CYP3A4/5, which was confirmed in an *in vivo* DDI study with a strong CYP3A4/P-gp inhibitor, itraconazole, in which the GMRs for C_{max} and $AUC_{(0-\infty)}$ of bardoxolone methyl were 6.9 and 8.7, respectively, when bardoxolone methyl was co-administered with itraconazcole as compared to alone. Based on the PBPK model, a slight increase in the exposure of bardoxolone methyl was predicted when co-administered with mild CYP3A4 inhibitor. There are uncertainties with the PBPK model and therefore a larger increase in the exposure of bardoxolone methyl (>20-30%) cannot be ruled out.

No CYP3A4 *in vivo* induction study has been performed. The PBPK model was not adequately qualified, and therefore cannot be used to predict the effect on bardoxolone methyl when co-administered with a CYP3A4 inducer. Since bardoxolone methyl seems to be mainly metabolized by CY3A4/5, an effect on the pharmacokinetics is expected when administered with a strong CYP3A4 inducer.

Other CYPs enzymes is also involved in the metabolism, although the total contribution is much smaller than CYP3A4/5. Of these enzymes, CYP2C9 seem to contribute more to the overall elimination.

The *in vitro* studies performed to evaluate if Bardoxolone methyl is a substrate for P-gp, BCRP, OATP1B1 and OATP1B3 transporters are inconclusive, since the concentrations of bardoxolone methyl were much higher than the therapeutic concentrations at steady state.

Bardoxolone methyl as perpetrator

Cut-off concentrations for bardoxolone methyl, for the evaluation of interaction potential *in vivo*

50×$C_{max(u)}$[a] (µM)	**25×Inlet $C_{max(u)}$[b]** (µM)	**0.1×Dose/250 ml[c]** (µM)
0.1	8.7	23.7

a. calculated as C_{max} x fu. C_{max} = 0.036 µM [18 ng/mL], predicted mean C_{max} in the Phase 2 and Phase 3 in study 1603, following once daily oral administration of 30 mg Imbarkyd. Human fu = 0.056. Mw=505.70 g/mol.
b. calculated as [fu,b × ([I]max,b + (Fa × Fg × ka × Dose/QH))]; where fu,b is calculated as [fu/(Cb/Cp)] where Cb/Cp =0.6, [I]max,b is determined as (C_{max} x Cb/Cp), ka = 0.1 min-1, dose = 30 mg/day, Fa x Fg = 1 (worst case scenario) and QH = 1600 ml/min.
c. Calculated using the clinical dose of 30 mg (on a molar basis) in a volume of 250 mL

In vitro studies indicated that bardoxolone methyl is not an inhibitor (direct, time-dependent or metabolism-dependent) of CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6. This (absence of direct inhibition) is supported by a clinical study in which no clinically relevant differences in the systemic exposure of midazolam (CYP3A4 substrate) and repaglinide (CYP2C8 substrate) were observed when these substrates were co-administered with a single dose of bardoxolone methyl as compared to alone.

Bardoxolone methyl inhibited P-gp and BCRP *in vitro*. No clinically relevant differences in the systemic exposure of rosuvastatin (BCRP substrate) and digoxin (P-gp substrate) were observed in the *in vivo* DDI study when these substrates were co-administered with bardoxolone methyl as compared to alone. Bardoxolone methyl was not an inhibitor of BSEP, OCT1, OCT2, OAT1, OAT3, OATP1B1, OATP1B3, MATE1 and MATE2-K *in vitro*.

The CYP1A2, CYP3A4 and CYP2B6 *in vitro* induction studies are inconclusive since they were not performed in accordance with the EMA DDI guideline, in which it is recommended to measure the extent of enzyme induction at mRNA level.

M3 and M19 as perpetrator

In vitro studies were performed to assess whether the metabolites, M3 and M19, are inhibitors of different CYP enzymes and transporter proteins.

The IC50 for direct inhibition of the CYP enzymes studied (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4/5), were > 30 µM (the highest concentration studied). Metabolism-dependent inhibition was observed for M3 for CYP3A4/5.

Exposure relevant for safety evaluation

For bardoxolone methyl following 30 mg/day in study 402-C-1603P3, AUC0-24h at steady state was predicted to be 223 ng*h/mL and $C_{max,ss}$ 17 ng/mL, see Table 7.

3.3.1.2. Pharmacodynamics

Mechanism of action

Bardoxolone activates the Keap1-Nrf2 pathway by selectively and reversibly binding to Keap1, thereby causing a conformational change in Keap1, preventing degradation of Nrf2 and leading to Nrf2 activation. Nrf2 is a transcription factor that translocates to the nucleus and binds to highly specific promoter regions of DNA called antioxidant response elements (AREs), which subsequently leads to transcriptional induction of hundreds of target genes.

The Keap1-Nrf2 pathway plays a key role in the resolution phase of inflammation by regulating the expression of genes involved in redox balance, mitochondrial metabolism, and inflammatory cytokine production. Genetic research data in humans demonstrate that the Keap1-Nrf2 pathway is suppressed in many forms of CKD, including Alport syndrome, and is an important correlate with glomerular filtration rate (GFR) (Martini et al; J Am Soc Nephrol 2014;25:2559-72). Nrf2-knockout mice further demonstrate that Nrf2 is necessary for protection against oxidative stress and inflammation in the kidney. For example, aged Nrf2-knockout mice develop a lupus-like autoimmune nephritis (Yoh, 2001), and histologic analyses of kidneys show enlarged glomeruli, mesangial cell proliferation, thickening of the glomerular basement membrane, and glomerulosclerosis that is associated with impaired antioxidative activity and increased oxidative damage (Ma, 2006). In contrast to mice with genetic ablation of Nrf2, mice that have a genetic knockdown of Keap1 and, thereby, enhanced constitutive activation of Nrf2, have markedly increased protection against renal insults. For example, Keap1-knockdown mice have improved renal function 3 days after ischemia-reperfusion injury (Tan, 2016).

Primary and Secondary pharmacology

The pharmacodynamic properties of the product is mainly characterised in a non-clinical setting.

The principal clinical pharmacodynamic parameter for bardoxolone is eGFR. Changes in eGFR from baseline is also the primary efficacy variable in the main Alport clinical Study 1603 and therefore further discussed in the Clinical Efficacy section below.
A Phase 2 pharmacodynamic study on eGFR and a phase 1 pharmacokinetic and pharmacodynamic study in patients with chronic kidney disease (CKD) and type 2 diabetes were performed (Study 005 and 1102). Both studies were terminated early for safety reasons related to the BEACON study. A thorough QT-study (Study 1006) was performed in healthy subjects.

Study 1102 was a Phase 1, multicentre, open-label, non-randomised, multiple-dose study to assess the PK profile, PD response, iron stores, kidney function, and inflammation biomarkers following 56-day (8 weeks) treatment with bardoxolone methyl in adult patients with T2DM CKD. A total of 24 patients were enrolled and received 20 mg bardoxolone methyl PO QD. However, only 15 patients had evaluable PK and PD data at study termination due to early termination.
There was an increase from baseline in eGFR values with bardoxolone methyl treatment in all study subgroups groups, i.e., CKD 3b, CKD 4, UACR <300 mg/g and UACR ≥300 mg/g (mean increase of 5.32 to 10.6 mL/min/1.73 m2 across groups on Days 28 and 56). After cessation of dose administration, eGFR values tended to return to baseline in all study groups.

Study 005 was a phase 2, randomised, double-blind, placebo-controlled study. Subjects with CKD 3 (N=120) were randomly assigned to receive either bardoxolone methyl (N=65) or placebo (N=55) at a 1:1 ratio, and subjects with CKD 4 were assigned at a ratio of 2:1. Study drugs (bardoxolone methyl or placebo) was orally administered once daily for 16 weeks with dose escalation from 5 mg to 15 mg. At the early termination of the study, 19 subjects in the bardoxolone methyl group and 25 subjects in the placebo group had results from Week 16.
The primary efficacy variable was change from baseline in GFR at 16 weeks after the start of study drug administration. At study termination, the primary efficacy variable was 5.86 (2.58, 9.13) mL/min/1.73 m2 in the bardoxolone methyl group, -0.46 (-3.32, 2.39) mL/min/1.73 m2 in the placebo group. The difference in LS means between the bardoxolone methyl group and the placebo group was 6.32 mL/min/1.73 m2 and improvements were seen in GFR in the bardoxolone methyl group. In addition, results of analysis of all subjects and analysis by CKD stage using FAS (secondary analysis), showed improvements in the bardoxolone methyl group in changes from baseline in eGFR at 16 weeks after the start of study drug administration in both subgroups of CKD 3 and CKD 4.

Study 1006 was a Phase 1, single-centre, multiple-dose, randomised, double-blind, double-dummy, placebo-controlled, active-comparator, parallel study of bardoxolone methyl to evaluate its effect on cardiac repolarisation and to characterise its multiple-dose PK in healthy adult subjects. A total of 179 subjects were randomised to one of the following treatments:

- 20 mg bardoxolone methyl PO QD for 6 days (therapeutic dose; N = 45)
- 80 mg bardoxolone methyl PO QD for 6 days (supratherapeutic dose; N = 44)
- Placebo PO QD for 6 days (placebo; N = 45)
- Single dose 400 mg moxifloxacin PO on Day 6 (active comparator; N = 45)

A small dose-dependent increase in heart rate was observed in bardoxolone treated subjects but blood pressure was unaffected.

Administration of the therapeutic dose of 20 mg and a supratherapeutic dose of 80 mg bardoxolone did not increase QT calculated by either Fridericia's formula (QTcF) or individual corrections (QTcI). Rather, there was a slight trend for shortening of the QT-interval at higher plasma concentrations. In the non-clinical studies performed in cynomolgus monkeys, a reduction in QTc was observed. In this study, increased QRS and PR was also observed. QRS and PR from the thorough QT study has not been presented in a comprehensive way and is not discussed in the application. The applicant is requested to provide a discussion on all ECG parameters from the thorough QT study in relation to the previous findings in the cynomolgus monkeys taking into account that C_{max} achieved during the supratherapeutic dose was only slightly higher than $C_{max,ss}$ at the highest recommended dose (30 mg once daily) in patients.

Relationship between plasma concentration and effect

The final population PK model was used to derive individual exposure (plasma concentration) predictions used in the exposure-response analyses given individual dosing records.

eGFR Disease Progression Model

Longitudinal exposure-response (ER) analysis was performed for the effect of bardoxolone methyl on the time course of renal function in Studies 1603 Phase 2 and 1603 Phase 3. The potential impact of bardoxolone methyl exposure and covariates (age, sex, and race on the rate of disease progression and drug effect slope) on Alport syndrome disease progression, as measured by eGFR, was evaluated.

The eGFR disease progression ER analysis dataset included 2430 eGFR measurements from 187 patients with Alport syndrome aged 13 to 70 years old, 109 (58%) of which were female, and 144 (77%) of which were of white race. Of the 187 patients, 80 (43%) received placebo and 107 (57%) received bardoxolone methyl.

An ER relationship was established for the effect of bardoxolone methyl concentration on the time course of renal function with the following conclusions:

- Alport syndrome eGFR disease progression was approximated by an exponential function parameterised for the baseline status and rate of disease progression.
- Drug effect was modelled as a power function asserting that an increase in eGFR is proportional to the bardoxolone methyl concentration in plasma.
- Age was identified as a statistically significant covariate on rate of disease progression. For patients aged ≤30 years, kidney function was deteriorating at a faster rate compared to patients aged >30 years.

Longitudinal Alanine Aminotransferase and Aspartate Aminotransferase Models

Longitudinal ER analysis was performed for the effect of bardoxolone methyl on the time course of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in Studies 0903, 1302, 1603 Phase 2, 1603 Phase 3 Year 1, and 1702. The potential impact of bardoxolone methyl exposure and disease population (Alport syndrome/ADPKD/FSGS/IgAN/T1DM CKD vs T2DM CKD/PAH) on ALT and AST concentrations was evaluated.

The longitudinal ALT and AST analysis datasets included 22530 ALT and 22459 AST measurements from 2641 patients aged 13 to 93 years, 1411 (53%) of which were male, and 2053 (78%) of which were of white race. Of the 2641 patients, 2185 (83%) had T2DM CKD, 187 (7%) had Alport syndrome, 166 (6%) had PAH, 75 (3%) had other rare CKDs (ADPKD, FSGS, or IgAN), and 28 (1%) had T1DM CKD. Of the 2641 patients, 1177 (45%) received placebo and 1464 (55%) received bardoxolone methyl.

ER relationships were established for the ALT and AST time course following bardoxolone methyl administration and supports the following:

- The rate of increase in ALT was disease population dependent. Patients with Alport syndrome, ADPKD, FSGS, IgAN, or T1DM CKD had a 2.65-fold increase in ALT level as a result of bardoxolone methyl treatment relative to patients with T2DM CKD or PAH.
- The rate of increase in AST was disease population dependent. Patients with Alport syndrome, ADPKD, FSGS, IgAN, or T1DM CKD had a 3.97-fold increase in AST level as a result of bardoxolone methyl treatment relative to patients with T2DM CKD or PAH.

Logistic Regression Exposure-Response Analyses

Logistic regression ER analysis was performed for the incidence of potential fluid overload-related events and muscle spasm events in Studies 0903, 1302, 1603 Phase 2, 1603 Phase 3 Year 1, and 1702. The potential impact of bardoxolone methyl exposure and other predictors (age, sex, race, concomitant PPI, concomitant CYP450 inhibitors, and disease population group) on the adverse event incidence rates were evaluated.

The logistic regression ER analysis dataset included 2536 patients aged 13 to 93 years, 1366 (54%) of which were male, 1966 (78%) of which were of white race, 1575 (62%) of which did not have concomitant PPI use, 1938 (76%) of which did not have any concomitant CYP450 inhibitor use. Of the 2536 patients, 1228 (48%) received placebo, 1308 (52%) received bardoxolone methyl, 736 (29%) had a potential fluid overload-related event, and 757 (30%) had a muscle spasm event.

Exposure-response relationships were established between bardoxolone methyl exposure and the incidence rates of potential fluid overload-related events and muscle spasm events and support the following:

- The probability of a potential fluid overload-related event is correlated with increasing bardoxolone methyl C_{max} and with concomitant PPI and CYP450 inhibitors relative to the reference patient receiving placebo without concomitant PPI or CYP450 inhibitors.
- Overall, the model-predicted probabilities of potential fluid overload-related events were low and were estimated to be <29% at a bardoxolone methyl C_{max} of 10.7 ng/mL (90^{th} quantile of observed data) compared to 22.2% for placebo.
- The probability of a muscle spasm event is correlated with increasing bardoxolone methyl C_{max} and with decreasing age relative to the reference patient who is 65 years of age and receiving placebo.

It should be noted that the patients with T2DM CKD, a population at inherently greater risk of fluid overload, comprised a disproportionate majority of subjects in the logistic regression ER analysis dataset.

3.3.2. Discussion on clinical pharmacology

Pharmacokinetics

The applicant has performed a number of clinical pharmacology studies to describe the pharmacokinetics and elimination of bardoxolone methyl, and to identify special populations or drug-drug interactions with risks for altered drug exposure. The PK of bardoxolone methyl is in general acceptably characterised except the metabolite ID characterisation. Bardoxolone methyl is extensively metabolised but inadequate studies has been performed in order to identify major and/or active metabolites and further investigations are requested as a major objection.

The applicant should discuss the therapeutic window of bardoxolone methyl and try to define exposure range within which no clinically meaningful changes are expected with regards to efficacy and safety. With respect to weak CYP3A4 inhibitors and weak CYP3A4 inducers, further justification is sought that bardoxolone methyl could be administered without extended monitoring or dose adjustments.

The long-term stability has not been adequately justified in the bioanalytical methods since the acceptable storage time interval in the validation reports are 228 days (150927VEMB_RIT_R1Method - Q2 solutions) and 182 days (R&D/12/312 Method-AbbVie), but values of 571 days and 350 days, respectively, are reported in 2.7.1 (Summary of biopharmaceutic studies and associated analytical

methods). However, no validation report was provided to support the updated long-term stability. Moreover, in several studies the maximum storage period between blood sampling and sample preparation exceeded even this updated long-term stability, i.e. 581 day in study 0903, 867 days and 1102 days in study 1302 (AbbVie and Q2 Solutions method). The applicant is asked to provide long-term stability data that cover the maximum storage periods in the respective studies.

The applicant should justify that there is no inter-conversion of bardoxolone methyl to any of the epimers (diastereomers) *in vivo*.

Population PK analysis

A pooled population PK analysis with various disease populations and dosing regimens was used to describe the impact of intrinsic and extrinsic factors on bardoxolone methyl PK which is accepted. It is noted, however, that the proportion Alport syndrome patients in the dataset was small (6%) while majority (70%) were patients having T2DM CKD with significantly higher median age (64.8 years) compared to an average patient with Alport syndrome (40.5 years). Given the relatively small representation of actual target population, the applicant is asked to discuss how is the model representative for describing PK in patients with Alport syndrome. In general, standard model development and evaluation methodology was used. It is noted that the sampling importance sampling (SIR) method was used to derive parameter uncertainty. The use SIR was a deviation from the analysis plan, and it is not clear why this change in method was made. Unexpectedly low parameter uncertainty is noted for CL/F and Tlag so further description of the SIR methodology is sought. It should be clarified if the covariance matrix from the final popPK model was used in SIR, and graphs for visual inspection should be provided. The pcVPC seems to indicate that the Alport syndrome patients (study 1603P2 and 1603P3) could be sufficiently well predicted. However, to be able to thoroughly assess the model performance updated pcVPCs (predictions vs time since last dose, with and without observations) should be provided. Overall, the covariate modelling is accepted. However, due to the unbalanced proportion of different disease populations in the dataset, the disease effect should be interpreted with caution as it could be reflective of different study designs rather than disease. The different diseases were lumped into two categories: reference (Alport syndrome/T2DM CKD/PH) vs Disease Population 2 (healthy/T1DM CKD/ADPKD/FSGS/IgAN/hepatic impairment). The applicant is asked to clarify this division and to explain why Alport syndrome as a target disease population was not tested as a covariate by itself. The applicant is asked to present inter-individual variability in the plasma exposure (e.g., C_{max} and AUC), expressed as CV%, from the Pop-PK analysis.

Physiologically Based Pharmacokinetic Analysis

To assess the effect of weak, moderate, and strong CYP3A4 inhibitors and moderate and strong CYP3A4 inducers on bardoxolone methyl PK and support dosing recommendations, a PBPK model for bardoxolone methyl was developed and used to predict exposures in the absence and presence of CYP3A4 DDI perpetrators.

The PBPK model input parameters, based on *in vitro* and *in vivo* data, seem reasonable. The fmCYP3A4/5 value was evaluated to improve model prediction however an fmCYP3A4/5 of 84.5%, corresponding to *in vitro* data, was used in the final model.

Three clinical studies were used to verify the model predictions, including one study with DDI information (itraconazole study 1701). It is noted however, that only bardoxolone single dose data has been used in the verification which is somewhat limiting. Furthermore, no 30 mg doses were used in the PBPK model development introducing an uncertainty of model predictions (simulations) at high exposures. Since strong and moderate inhibitors are contraindicated this model deficiency is not further pursued.

Overall, the bardoxolone PK profile is fairly well predicted although there seems to be a tendency for over prediction of CL (i.e., under prediction of AUC). The PK predictions with itraconazole (strong CYP3A4/5 inhibition) is well predicted. The predictions of the itraconazole study can be viewed as a worst-case scenario, thus the model is considered adequate for predictions of CY3A4/5 inhibition. However, only one weak CYP4A4/5 inhibitor has been used in the simulations, introducing an uncertainty about the generalisability of the results. As a sensibility analysis, it would have been preferred to simulate DDI results with several weak inhibitors.

No model verification has been provided for CYP3A4/5 induction; thus the model is not considered applicable for simulations of CYP3A4/5 induction.

ADME

The absorption and distribution characteristics of bardoxolone methyl have in principle been sufficiently described, but some questions are raised regarding the 20 mg capsule strength, food intake and plasma protein binding.

Several clinical pharmacology studies that are key for description of bardoxolone methyl PK used a single 20 mg capsule (evaluation of food effect, mass balance, bardoxolone methyl as a perpetrator of DDIs, hepatic impairment). A comparative bioavailability study comparing exposures between administration of two capsules versus a single capsule providing a dose of 10 mg or 30 mg showed inequivalence for the higher dose. No such comparison was made between 5 mg + 15 mg capsule versus single 20 mg capsule. It should be demonstrated that the results obtained from studies using single 20 mg capsule are applicable also when 20 mg dose is taken as one 5 mg capsule + one 15 mg capsule (use intended post-marketing); i.e. a comparative bioavailability study between 1x20 mg capsule and 1x5 mg + 1x15 mg capsules is recommended.

Regarding concomitant food intake, there was no change in AUC when administered with high-fat food and the study drug was administered in accordance with SmPC recommendations in the efficacy studies in Alport syndrome. The applicant concludes that the 1.7-fold increase in C_{max} and later t_{max} following single dose with high-fat meal compared to fasted state is not clinically meaningful. However, it should be further justified that such an increase in C_{max} will not influence safety of the product, especially since, according to the applicant, higher C_{max} has been related to fluid overload and muscle spasms.

Bardoxolone methyl is approximately 94% bound to human plasma proteins. Protein binding was not concentration dependent in the concentration range tested (10 -100 ng/mL). Though, concentration range tested was somewhat higher than the expected therapeutic concentrations (below 10 ng/mL at lower doses than 30 mg QD) and the protein binding tests for bardoxolone methyl should be redone with the relevant therapeutic concentration range, unless otherwise justified. The applicant is also asked to clarify how was the value of Vc/F of 33 L/kg stated in the SmPC obtained.

There are several questions regarding metabolism and excretion of bardoxolone methyl with a major objection raised regarding that the metabolism of bardoxolone methyl is not sufficiently described.

The largest metabolite identified in the plasma samples from the mass balance study is thiocyanate (76%). Also in urine, thiocyanate was the only identified metabolite. Metabolites resulting from the decyano metabolism were not identified which leads to a large gap of knowledge since these possible metabolites are unlabelled in the mass balance study. The 14C-labelling in the nitril-moiety is therefore not an adequate position since information regarding metabolites remaining after decyanation is missing. Unknown metabolites lacking the nitril moiety could exist and the amount of the metabolites could be >10% of total drug-related exposure if a study is performed with bardoxolone methyl labelled in another position. Characterisation of the metabolites regarding pharmacological activity should be

performed and investigation of pharmacokinetics could be necessary if there are any active metabolites identified. The amount of the metabolites M3 and M19 could be >10% of total drug-related exposure if a study is performed with bardoxolone methyl labelled in another position and other metabolites lacking the nitril moiety is identified. The amount (in %) of M3 and M19 is depending on which metabolites that are identified and if the distribution to plasma of the unknown metabolites is different than the distribution of thiocyanate. Since the amounts of metabolites is relative and not absolute when calculated as % of total drug-related exposure, the amounts of M3 and M19 could then be >10% and more characterization of the metabolites M3 and M19 could be necessary.

The metabolism of bardoxolone methyl is not sufficiently described, and it is unclear if there are additional major and/or active plasma metabolites that need further preclinical, pharmacological and pharmacokinetic characterisation. The metabolism of bardoxolone methyl needs to be further investigated. New studies to evaluate the metabolism of bardoxolone methyl are needed to conclude if there are any major and/or active metabolites.

The applicant concludes that the carboxylic acid metabolites (C17-metabolites) cannot be identified in human plasma samples or in human *in vitro* incubations. This is not completely agreed due to the inadequate *in vitro* metabolism data and since no sodium sulphite had been added to the analysed *in vivo* plasma samples (from study RTA402-C-0801). The applicant is asked to discuss how the lack of sodium sulphite affect the metabolite profile in plasma, what has happened ex vivo in the plasma samples and if this could possibly change the conclusion that no C17-metabolites were identified in the plasma samples from day 56 in study RTA402-C-0801.

The metabolite ID result in urine was from the last collection interval (288-312 hours) and not necessary representative for earlier time points. The applicant is asked to discuss why not any earlier urine samples were included in the metabolite ID evaluation and to reassess the conclusions regarding metabolites in urine.

The mass balance study is not optimally designed due to the position of the labelling in the cyanogroup. The excretion routes for possible unidentified (non-labelled) metabolites related to the decyano biotransformation is unknown and also the total mass balance cannot be concluded from the submitted results. The results do however indicate that liver metabolism, followed by biliary excretion of the metabolites is the primary route of elimination for bardoxolone methyl. The results from the human mass balance and the suggested excretion routes needs to be discussed and re-evaluated including discussion regarding the excretion routes of possible unidentified metabolites related to the decyano metabolism. The applicant is also asked to discuss if a new human mass balance study with Bardoxolone methyl 14C-labelled in a more adequate position is necessary.

In the SmPC section 5.2, it is stated that the apparent terminal half-life of bardoxolone methyl is estimated to be between 20 and 48 hours. According to Table 5, the plasma half-life is between 19 and 85 hours. The value of the half-life should be changed to 19-85 hours if not adequately justified.

Special populations

The effect of renal impairment on bardoxolone methyl was evaluated in the population PK analysis and no dedicated renal impairment study was performed. The PopPK analysis dataset included a representative distribution of eGFR values; median(range) 26.0 (9.00, 147) mL/min/1.73 m².

Results from the mass balance study show that renal elimination is not an important elimination pathway for unchanged bardoxolone methyl. However, it was the principal elimination pathway for thiocyanate metabolite. According to the EMA guideline on renal impairment (EMA/CHMP/83874/2014), a dedicated study in at least subjects with severe RI should be conducted even for non-renally eliminated drugs due to possible effects of renal impairment on non-renal elimination mechanisms.

This is of even more importance for bardoxolone methyl since it is intended for the treatment of Alport syndrome, a state inherently associated with decreased renal function.

The PK of bardoxolone methyl was evaluated in several studies including population with varying degrees of renal impairment. However, most of these studies employed only sparse sampling, there was a lack of healthy matched control, no measurements of the fraction unbound and no measurement of thiocyanate levels.

With bardoxolone methyl being highly protein bound (94%) any changes in the fraction unbound as a consequence of RI could have a significant impact on unbound exposure. Thiocyanate metabolite is mainly excreted via urine. If the elimination of thiocyanate is significantly reduced by the renal impairment this could potentially lead to its toxic plasma levels. Moreover, there is a potential risk of accumulation of still unidentified metabolites. Given the above, the applicant should further justify lack of a dedicated RI study.

A hepatic impairment study has been performed and the mean total plasma exposure ($AUC_{0-\infty}$) of bardoxolone methyl following a 20 mg oral dose was approximately 38%, 84%, and 79% higher in subjects with mild, moderate, and severe hepatic impairment, respectively, as compared with subjects with normal hepatic function. The terminal plasma half-life is prolonged with increased severity of hepatic impairment. Hepatic impairment does not appear to alter C_{max}. The recommendation in the SmPC that Imbarkyd should be used with caution in patients with mild hepatic impairment and that Imbarkyd is not recommended for use in patients with moderate or severe hepatic impairment is acceptable.

Information regarding prolonged half-life in patients with moderate and severe hepatic impairment compared to patients with normal hepatic function is suggested to be included in the SmPC, section 5.2.

Sex and body weight were not significant covariates in the Pop PK model, hence no dose adjustments based on sex or body weight are necessary. However, due to the inclusion of the adolescent population in the sought indication some further detail of the potential influence of body weight (in particular low body weight) is requested.

Race

The majority of subjects in the PopPK analysis dataset were of white race (71%), 17% were Black/African American and 7% were Asian. Based on the Pop PK analysis, Black/African American subjects showed approximately 30% decrease in bardoxolone methyl exposure (C_{max} and AUC_{ss}) compared to a reference subject. When data from the Japanese study 005 were introduced in the population PK analysis, the analysis estimated approximately 30% higher exposure in Asian subjects. The applicant claims that these differences are not considered clinically meaningful because subgroup analysis by race did not show significant effect of race on clinical efficacy or safety. It should be noted that the number of Black/African American subjects (n=6) and number of Asian subjects (n=14) in these analyses was rather limited. For assessment of subgroup analyses, the reader is referred to subsequent sections of the AR. The applicant is asked to discuss the possible underlying reason for observed differences in the exposure between different races/ethnicities.

Age

Median age of subjects included in the population PK dataset was 65 years (range 13 to 92.4 years), which is significantly higher than the median age of patients with Alport syndrome (40.5 years). Age was not a significant covariate in the Pop PK model and simulated steady-state exposures between younger (<18 years) and older subjects (≥18 years) were similar. It should be noted that the number of adolescent subjects included in the analysis dataset was limited (n=13) and the results should be

interpreted with caution. The applicant is asked to extend this analysis also to elderly subjects (≥65 years) in order to show there are no significant differences in the exposure and to support the statement in section 4.2 that no dose adjustment is needed. Phase 2/3 study 1603 included 25 adolescent subjects (12 to 18 years of age). Two adolescents in Phase 2 and 11 adolescents in Phase 3 portion of the study received bardoxolone methyl and had their trough levels measured at week 12.

Interactions

Bardoxolone methyl as victim

The results from the *in vivo* DDI study with a strong CYP3A4/P-gp inhibitor, itraconazole, in which the GMRs for C_{max} and $AUC_{(0-\infty)}$ of bardoxolone methyl were 6.9 and 8.7, respectively, when bardoxolone methyl was co-administered with itraconazcole as compared to alone support that concomitant administration of bardoxolone methyl with moderate and strong CYP3A4 inhibitors is contraindicated. There are no SmPC restrictions regarding the use of mild CYP3A4 inhibitors. Based on the PBPK model, a slight increase in the exposure of bardoxolone methyl was predicted when co-administered with mild CYP3A4 inhibitor. There are uncertainties with the PBPK model and therefore a larger increase in the exposure of bardoxolone methyl (>20-30%) cannot be ruled out. The claim that the effect of mild CYP3A4 inhibitors is not expected to be clinically relevant should be further justified by the applicant.

No CYP3A4 *in vivo* induction study has been performed and the PBPK model was not adequately qualified, and therefore cannot be used to predict the effect on bardoxolone methyl when co-administered with a CYP3A4 inducer. Since bardoxolone methyl seems to be mainly metabolized by CY3A4/5, an effect on the pharmacokinetics is expected when administered with a strong CYP3A4 inducer, and therefore it is supported that concomitant administration with moderate or strong CYP3A4 inducers should be avoided. However, in 4.5 in the SmPC it is stated that treatment with bardoxolone methyl should be interrupted if treatment with moderate and strong CYP3A4 inducers cannot be avoided. This is not agreed. Treatment with bardoxolone methyl can continue. However, it is important that it is clear in the SmPC that concomitant treatment with moderate and strong inducers results in loss of efficacy. The information regarding the discontinuation of treatment with bardoxolone methyl should be removed from the SmPC. Caution is recommended for concomitant treatment with mild inducers. Further discussion and justifications are needed to support that there will be no clinically relevant loss of efficacy when bardoxolone methyl is co-administered with a mild CYP3A4 inducer.

Other CYPs enzymes is also involved in the metabolism, although the total contribution is much smaller than CYP3A4/5. Of these enzymes, CYP2C9 seem to contribute more to the overall elimination.

A new *in vitro* study performed at relevant concentrations to evaluate if Bardoxolone methyl is a substrate for P-gp, BCRP, OATP1B1 and OATP1B3 transporters is requested.

Bardoxolone methyl as perpetrator

The results from the *in vitro* and *in vivo* CYP inhibition studies shows that substrates of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 can be co-administered with bardoxolone methyl.

Substrates of BSEP, OCT1, OCT2, OAT1, OAT3, OATP1B1, OATP1B3, P-gp, BCRP, MATE1 and MATE2-K can be co-administered with bardoxolone methyl.

The CYP1A2, CYP3A4 and CYP2B6 *in vitro* induction studies are inconclusive since they were not performed in accordance with the EMA DDI guideline, in which it is recommended to measure the extent of enzyme induction at mRNA level. A new *in vitro* induction study, in which the extent of enzyme induction should be evaluated at mRNA level, is requested.

Treatment with ACEi/ARB is considered standard of care for patients with Alport syndrome and those medications have been used concomitantly with bardoxolone methyl in the Phase 3 study and are expected to be used concomitantly in the clinical practice. The applicant should provide a discussion regarding the potential for PK and PD DDIs between those co-medications.

M3 and M19 as perpetrator

In vitro studies were performed to assess whether the metabolites, M3 and M19, are inhibitors of different CYP enzymes and transporter proteins. The IC50 for direct inhibition of the CYP enzymes studied (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4/5), were > 30 µM (the highest concentration studied). Metabolism-dependent inhibition was observed for M3 for CYP3A4/5. However, the steady state plasma concentrations of the metabolites at the proposed posology in patients, and consequently the risk of inhibition *in vivo*, are unknown. The evaluation of the DDI potential of these metabolites is dependent on the response to MO. If these metabolites will be defined as major i.e., the AUC of the metabolite ≥ 25% of the parent drug and the AUC the metabolite is ≥ 10% of the total AUC of drug related material, the plasma concentrations of these metabolites at therapeutic doses and the cut-offs for systemic interaction should be determined, and the clinical relevance of these *in vitro* results should be discussed. Depending on the results, further *in vitro* evaluation of the TDI-signals might be needed to determine K_I and k_{inact}.

Since there is no guideline requirement to study the effect of the major metabolites on the transporters, and that the systemic exposure of M3 and M9, is unknown, the results from the inhibition study will not be further evaluated.

Pharmacodynamics

The principal clinical pharmacodynamic parameter for bardoxolone is eGFR. Changes in eGFR from baseline is also the primary efficacy variable in the main Alport clinical Study 1603 and therefore further discussed in the Efficacy section below.

In summary, there was an increase in eGFR upon initiating bardoxolone in both Study 0005 and 1102. The same pattern was seen e.g., in the phase 3 BEACON study in subjects with type 2 diabetes and the main Phase 2/3 Alport study 1603 as discussed in the Efficacy section.

As adequately pointed out by the applicant, the rapid increase in eGFR upon bardoxolone initiation could be suspected to represent an increase in intraglomerular pressure, e.g., through impact on the efferent and/or afferent arteriole, or an increase in systemic blood pressure. In both cases, this may lead to long-term damage to the renal parenchyma and accentuated progress of renal impairment.

To address this, the applicant has conducted studies to characterize bardoxolone methyl's mechanism for increasing GFR in a non-clinical setting. According to the applicant, these data together with reports from the scientific literature indicate that bardoxolone methyl produces acute increases in eGFR by increasing glomerular surface area and by reversing endothelial dysfunction and mesangial cell contraction, thus restoring GFR of individual nephrons without changes in intraglomerular pressure. Clarifying questions on these novel mechanisms are raised elsewhere**.**

In the thorough QT-study (Study 1006), administration of bardoxolone did not increase QT. However, the applicant is requested to provide a discussion on other ECG parameters than QT, given findings of increased PR and QRS in the non-clinical studies.

Relationship between plasma concentration and effect

The applicant has provided a longitudinal analysis of eGFR and the influence of bardoxolone plasma concentrations based on data from study 1603. Standard methodology for longitudinal disease

progression modelling has been used, and in particular the use of plasma concentrations is acknowledged. However, since time-varying eGFR is a covariate in the population PK model the plasma concentrations cannot be considered independent of the effect and thus, confounding between exposure and response cannot be ruled out. Furthermore, due to the titration regimen and dose adjustments allowed in study 1603 the exposure-response information is limited, and further analyses are not considered meaningful.

The dataset used in the ALT and AST analyses comprised of pooled data from four different patient studies where most of the data (83%) comes from a T2DM CKD patient population and only 7% of data came from Alport syndrome patients (study 1603). Thus, the estimated disease effect should be interpreted with caution especially since no difference in ALT/AST between patient populations is anticipated. Furthermore, it is not clear why dose-response modelling were used in the longitudinal ALT/AST models instead of exposure-response. The results indicate that there is a dose dependent increase of ALT/AST in the beginning of the treatment which subsequently decrease over time. Thus, the results from the longitudinal dose-ALT/AST analyses support a dose titration regimen in combination with monitoring of ALT/AST levels for the first 12 weeks.

The exposure-safety analysis for fluid overload comprised of a pooled dataset with following the patient distribution: Alport (7%), PAH (6%), rare CKD (3%), T2DM (84%). A logistic regression analysis on the incidence of event was conducted, thus the timing of the event was not accounted for. In addition, the analysis has several limitations. First, it is not clear why concomitant PPI and CYP450 inhibitors as well as exposure are included in the analysis as concomitant medication is expected to have strong correlation with exposure. The population analysis report (REAT-PMX-BARD-1532) also states that the timing of concomitant medication is poorly documented, and the results should be interpreted with caution. Secondly, it is noted that the $C_{max,ss}$ distribution is somewhat skewed and steady state levels for C_{max} given a 20 mg or 30 mg dose (9.64 ng/mL and 17.2 ng/mL, respectively) is in the upper range of the C_{max} distribution increasing the uncertainty of the results. Furthermore, the applicant argues that the event rate is biased by the over representation of T2DM CKD patients that are of higher risk for fluid overload events. Nevertheless, observed data indicate no trend between fluid events and treatment (i.e. overlapping event rates between C_{max} quantiles and placebo. Overall, the exposure-fluid overload analysis should be interpreted with strong caution and additional modelling is not requested due to data limitations.

The logistic regression analysis for exposure-muscle spasms suffers from the same data limitation as described above for the fluid overload analysis with the exception of T2DM patient bias. Thus, the exposure-muscle spasm analysis should be interpreted with strong caution and additional modelling is not requested due to data limitations. Nevertheless, observed data indicate an increased risk of muscle spasm AEs with active treatment, however there is no clear increased risk with increasing C_{max} values.

3.3.3. Conclusions on clinical pharmacology

Pharmacokinetics

Bardoxolone methyl is extensively metabolised, but the metabolism is not sufficiently described. A major objection is raised regarding that the metabolism of bardoxolone methyl needs to be further investigated. New studies to evaluate the metabolism of bardoxolone methyl are needed to conclude if there are any major and/or active metabolites. Several other concerns have also been raised, see LoQ.

Pharmacodynamics

The pharmacodynamic properties of the product are mainly characterised in a non-clinical setting. The principal clinical pharmacodynamic parameter for bardoxolone is eGFR. Changes in eGFR from baseline

is also the primary efficacy variable in the main Alport clinical Study 1603 and therefore further discussed in the Efficacy section below.

Any QT-prolongating effect of bardoxolone is unlikely based on absence of prolonged interval in the thorough QT-study, however further information is requested on other ECG parameters.

Several exposure-efficacy and exposure-safety analyses have been investigated. However, all analyses suffer from various types of data and analysis limitations and should therefore be interpreted with strong caution. Overall, exposure-efficacy relationships cannot be determined on the available data and exposure-safety concerns can to some extent be mitigated with dose titration and monitoring.

3.3.4. Clinical efficacy

Efficacy data for bardoxolone for the *treatment of CKD caused by Alport syndrome in adults and adolescents aged 12 years and above* were obtained from three clinical studies (Table 8).

Table 8: Bardoxolone Methyl Clinical Studies in Patients with Alport Syndrome

Study ID	**Number of Enrolling Study Centers Locations**	**Study Start Status Enrollment/ Enrollment Goal**	**Study Design Objectives**	**Treatment(s)**	**Number of Patients by Treatment Arm**	**Duration**	**Gender (M/F) Median Age (Range)**	**Main Diagnosis Inclusion Criteria**	**Efficacy Endpoints**
Pivotal study: Study 1603 Phase 3	48 US, EU (France, Germany, Spain), Japan, Australia	24 Jul 2017 Completed; final DBL 06 Nov 2020 157/150	Randomised, placebo-controlled, double-blind, Phase 3 Efficacy and safety	Patients ≥18 years Bardoxolone methyl (dose titration: 5 mg to max 20 or 30 mg) or placebo, oral, once daily Patients <18 years Bardoxolone methyl (dose titration: 5 mg every other day to max 20 or 30 mg, once daily) or placebo, oral	Bardoxolone methyl = 77 Placebo = 80	104 weeks (two 48-week treatment periods, each followed by a 4-week off-treatment period)	Bardoxolone methyl : 34/43 43.0 (13, 65) Placebo: 32/48 43.0 (13, 70)	Alport syndrome confirmed by genetic testing or histological assessment Age 12 to 70 years Baseline eGFR: 30-90 mL/min/1.73 m^2 UACR: ≤3500 mg/g	Year 1 Primary: change from baseline in eGFR at Week 48 Key Secondary: change from baseline in eGFR at Week 52 following a 4-week off-treatment period Year 2 Primary: change from baseline in eGFR at Week 100 Key Secondary: change from baseline in eGFR at Week 104 following a 4-week off-treatment period
Open-label study: Study 1603 Phase 2	12 US	15 Feb 2017 Completed; final DBL 04 Oct 2019 30/30	Open-label Phase 2 Efficacy and Safety	Patients ≥18 years Bardoxolone methyl (dose titration: 5 mg to max 20 or 30 mg), oral, once daily Patients <18 years Bardoxolone methyl (dose titration: 5 mg every other day to max 20 or 30 mg, once daily), oral	Bardoxolone methyl= 30	104 weeks (two 48-week treatment periods, each followed by a 4-week off-treatment period)	12/18 48.5 (14, 59)	Alport syndrome confirmed by genetic testing or histological assessment Age: 12 - 70 years Baseline eGFR: 30-90 mL/min/1.73 m^2 UACR: ≤3500 mg/g	Primary: change from baseline in eGFR at Week 12 Secondary: change from baseline in eGFR at Week 48 and 100
Open-label extended access study: Study 1803	38 US, Japan, Australia	08 Mar 2019 Ongoing; interim DBL 18 Jan 2021 96/NA	Open-label, long-term extended access Phase 3a Long-term safety	Patients ≥18 years Bardoxolone methyl (dose titration: 5 mg to max 20 or 30 mg), oral, once daily Patients <18 years Bardoxolone methyl (dose titration: 5 mg every other day to max 20 or 30 mg, once daily), oral	Bardoxolone methyl = 96	Until bardoxolone methyl is commercially available	39/57 46.5 (15, 72)	Alport syndrome confirmed by genetic testing or histological assessment Patients who completed either Study 1603 Phase 3 or Study 1603 Phase 2	NA: eGFR was assessed as a safety analysis

The application is based on one pivotal trial (Study 1603 Phase 3 [CARDINAL Phase 3]), while the remaining two studies in patients with Alport syndrome are viewed as supportive (Study 1603 Phase 2 [CARDINAL Phase 2] and Study 1803/EAGLE). Given that a single pivotal trial is presented, considerations from *EMA Points to consider on application with 1. meta-analyses; 2. one pivotal study (CPMP/EWP/2330/99)* are relevant for this application.

3.3.4.1. Dose-response studies

There were no dose finding studies in subjects with Alport syndrome. The development program included three dose ranging studies (Studies 0801, 0804 and 0902), all in subjects with diabetes. However, only one study (Study 0902) used the amorphous SDD formulation intended for commercial use which was also used in the efficacy studies for Alport syndrome. Study 0902 is therefore considered most relevant to dosing in the Alport development program.

Study 0902

Study 0902 was a multi-centre, open-label, randomised, parallel group, dose-ranging, pharmacodynamic phase II trial to determine the effects of bardoxolone on eGFR in patients with Type 2 Diabetes (T2DM) and chronic kidney disease (eGFR 15-45 mL/min/1.73m2; CKD 3b-4). The study enrolled a total of 131 patients: 14 patients in the 2.5 mg group, 25 patients in the 5 mg group, 28 patients in the 10 mg group, 50 patients in the 15 mg group, and 14 patients in the 30 mg group. Treatment was given once daily for 84 days. The primary efficacy objective was the change from baseline in eGFR at Day 29 and the secondary efficacy objective was the change from baseline in eGFR at Day 85.

Mean eGFR over time is presented in Figure 6. The Primary efficacy analysis (Linear Trend Analysis – Day 29) is shown in Table 9. An ANCOVA analysis showed that the dose response was independent of baseline eGFR values (Table 9).

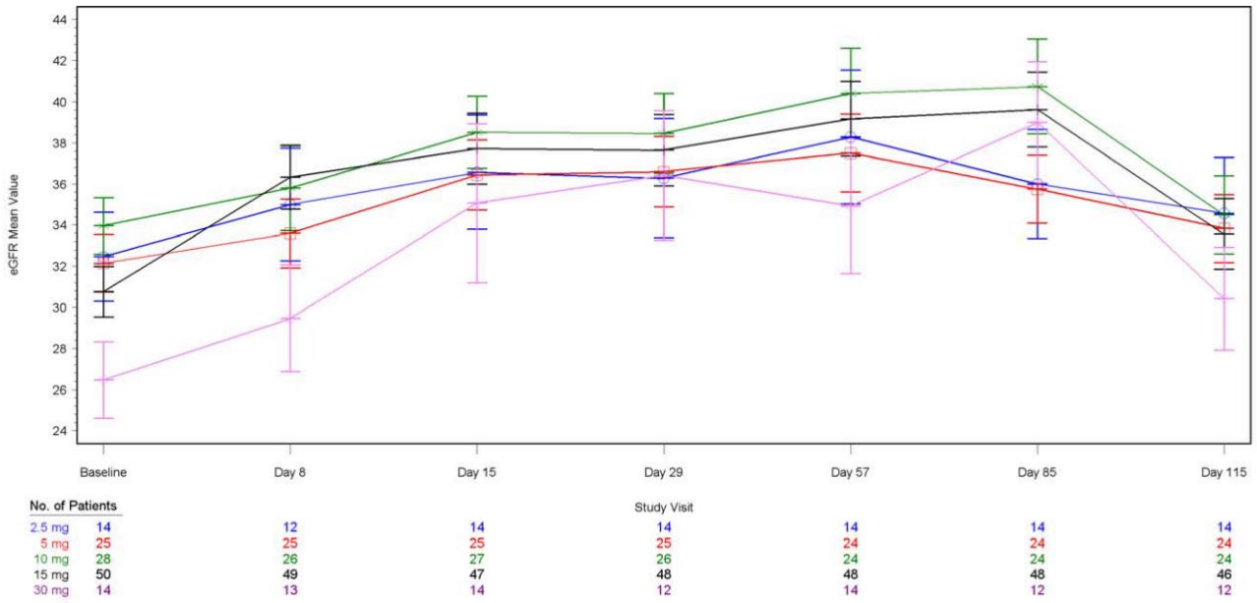


Figure 6: Mean eGFR (mL/min/1.73m2) by Study Visit and Dose Group – ITT Population

Table 9: Inferential Summary of the Change from Baseline in eGFR (mL/min/1.73m2) at Day 29 – ITT Population, Patients Randomized in First Enrolment Group

Day 29 (N=58)			
Model 1: ANOVA[a]			
Comparison	**Difference in LS Means (Δ)**	**95% CL of Δ**	**p-value[b]**
5 mg vs 10 mg	-0.1160	(-5.14, 4.91)	0.9632 [0.9365]
5 mg vs 15 mg	2.3214	(-2.86, 7.51)	0.3732 [0.2982]
5 mg vs 30 mg	7.1786	(1.99, 12.36)	0.0076 [0.0297]
Linear trend			0.0025 [0.0129]
Quadratic trend			0.6825 [0.9804]
Model 2: ANCOVA[c]			
Comparison	**Difference in LS Means (Δ)**	**95% CL of Δ**	**p-value[b]**
5 mg vs 10 mg	-0.1337	(-5.20, 4.93)	0.9580 [0.9320]
5 mg vs 15 mg	2.1568	(-3.15, 7.46)	0.4186 [0.3687]
5 mg vs 30 mg	6.8509	(1.32, 12.39)	0.0163 [0.0707]
Linear trend			0.0070 [0.0407]
Quadratic trend			0.6804 [0.9782]

The linear trend analysis indicates that the response in eGFR to bardoxolone was dose dependent. However, at Day 29, only the 30 mg arm was significantly different from the 5 mg arm, although a numerical trend to a better eGFR in the 15 mg compared to the 5 mg arm was seen. No statistical comparisons were presented at Day 85, i.e., the last day of treatment, but numerically, there was a dose dependent increase in eGFR also at Day 85. The results are considered in support of a dose of (15)-30 mg from an efficacy point of view

In the large phase 3 BEACON study (Study 0903) in subjects with type 2 diabetes (T2DM) and severe chronic impairment (CKD 4), the previously not investigated dose 20 mg once daily was used as fixed dose, in part based on study 0902. The applicant has not discussed whether the magnitude of effect from a given dose is possible to extrapolate between conditions. Notwithstanding, in the BEACON study, median Placebo-corrected change from baseline at week 48 was 6.4 mL/min/1.73 m2 compared to 9.5 mL/min/1.73 m2 in the pivotal study in Alport (Study 1603/Phase 3), indicating a similar treatment effect. The use of 20 mg can therefore be considered supported.

The patient population in three dose-ranging studies is quite different from the population with Alport syndrome. The degree of comparability between patients with different diseases (CKD in T2DM, diabetic nephropathy vs Alport syndrome) with respect to pharmacokinetic parameters influencing the optimal dose is unclear; however important differences seem plausible.

The applicant justifies different target doses in subjects with baseline urinary albumin/creatinine ratio (UACR) ≤300 mg/g and >300 mg/g with results from Studies 0902 and 0903. However, these data are not summarised and not easily assessable in the CSRs of Studies 0902 and 0903. The applicant is asked to present data supporting the differentiated dosing in a concise and assessable way**.**

Of note, fluid overload events were observed at doses of 20 mg in a subset of at-risk patients with Stage 4 CKD and T2DM, leading to pre-term closure of the BEACON study for safety issues (imbalance in subjects with heart failure). There were a higher proportion of serious adverse events (SAE) in the 30 mg arm of Study 0902 (4/14; 29%) compared to the other treatment arms (2.5 mg: 7%; 5 mg 16%, 10 mg 14%; 15 mg 8%) but the number of reports were low (n=1-4), and the proportion of SAEs reported was not dose dependent. In total, two SAEs of cardiac congestion were reported, one in the 10 mg arm and one in the 30 mg arm. It is agreed with the applicant that the result of Study 0902 does not indicate a worse outcome in the 30 mg arm.

3.3.4.2. Main study

"CARDINAL" trial: A Phase 2/3 trial for the efficacy and safety of bardoxolone methyl in patients with Alport syndrome

METHODS

Study Design

The CARDINAL-study included two cohorts: an open-label, Phase 2 cohort (Study 1603/Phase 2) and a subsequent Phase 3 cohort (Study 1603/Phase 3). Both studies are completed. Study 1603/Phase 3 was defined as the pivotal study.

Study 1603/Phase 3 was a double-blind, randomised, placebo-controlled study in male and female patients aged 12 to 70 years with Alport syndrome. Subjects were randomised 1:1 to bardoxolone or placebo. The primary analysis was performed at Week 48 and Week 100. A schematic view of the study is given in Figure 7.

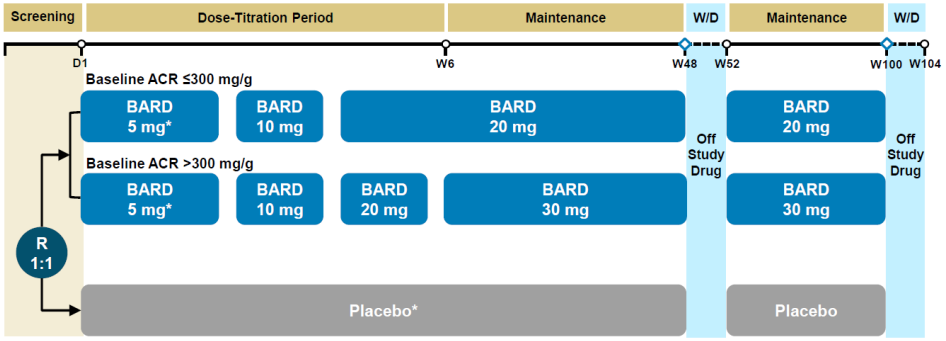


*Figure 7: Study design Pivotal Study 1603/*Phase 3

Study 1603/Phase 2 was open-label and uncontrolled, otherwise the study design was similar to that of the 1603/Phase 3 part of the study. Of note, subjects from the 1603/Phase 2 cohort could not enter the 1603/Phase 3 part of the study.

Study Participants

The same main eligibility criteria applied for 1603/Phase 2 and 1603/Phase 3.

Main inclusion criteria

- Male or female patients between 12 and 70 years old, inclusive, upon study consent.
- Diagnosed with Alport syndrome by genetic testing (documented mutation in a gene associated with Alport syndrome, including COL4A3, COL4A4, or COL4A5) or histologic assessment using electron microscopy.
- Screening eGFR (average of Screen A and Screen B eGFR values) ≥30 mL/min/1.73 m2 and ≤90 mL/min/1.73 m2. The two eGFR values collected at Screen A and Screen B visits used to determine eligibility must have had a percent difference ≤25%.
- Had a UACR ≤3500 mg/g at Screen B visit. Up to 50% of patients in Study 1603/Phase 2 and approximately 40% of patients enrolled in Study1603/Phase 3 could have had UACR of 301 mg/g to 3500 mg/g. Once enrolment of these patients was complete, the UACR inclusion criterion was ≤300 mg/g.

- Patients receiving an ACE inhibitor (ACEi) and/or an ARB should have been receiving the maximally tolerated labelled daily dose, for at least 6 weeks prior to the Screen A visit. The dosage of ACEi and/or ARB should have remained the same throughout the remainder of the study, and any potential changes were to be discussed with the medical monitor. Patients not currently taking an ACEi and/or ARB because they were not indicated or because of a medical contraindication may have been eligible provided the patient had not taken an ACEi and/or ARB at least 8 weeks prior to the Screen A visit

Main exclusion criteria

- Prior exposure to bardoxolone methyl.
- Ongoing chronic haemodialysis or peritoneal dialysis therapy, renal transplant recipient or acute dialysis or acute kidney injury within 12 weeks prior to Screen A visit or during Screening.
- BNP level >200 pg/mL at Screen A visit.
- Uncontrolled diabetes (haemoglobin A1c >11.0%) at Screen A visit.
- Serum albumin <3 g/dL at Screen A visit.
- History of clinically significant left-sided heart disease and/or clinically significant cardiac disease including, but not limited to, the following:
    - Clinically significant congenital or acquired valvular disease
    - Left ventricular ejection fraction <40% (based on echocardiogram performed at Screen A visit or within 6 months prior to Day 1)
    - Pericardial constriction (based on echocardiogram performed at Screen A visit or within 6 months prior to Day 1)
    - Restrictive or congestive cardiomyopathy (based on echocardiogram performed at Screen A visit or within 6 months prior to Day 1)
    - Symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or angina)
    - History of hospitalization for heart failure
    - Cardiac insufficiency, defined as New York Heart Association (NYHA) Class >II
    - History of atrial fibrillation
    - History of unstable arrhythmias

The eligibility criteria for eGFR and albuminuria are very broad, leading to marked variability in the disease manifestation and severity in the study population, i.e., anywhere from minimal disease without proteinuria and GFR close to 90 ml/min/1.73m2 to sub-nephrotic range proteinuria and GFR close to 30 ml/min/1.73m2. Furthermore, subjects with all genetic forms of Alport syndrome were eligible in the study. This further increases the variability of disease severity as subjects with Autosomal Recessive Alport syndrome (ARAS) and males with X-linked Alport syndrome (XLAS) have 100% lifetime risk of ESRD, while the risk for subjects with Autosomal Dominant Alport syndrome (ADAS) and females with XLAS is 20% and 25%, respectively. This is further discussed under subheading *Baseline data* below.

The inclusion of patients on stable ACE/ARB inhibitors is endorsed considering this is the current standard of care for patients with kidney disease. Requirements for receiving ACEi/ARBs were changed

two times, in protocol versions 2 and 3. In Protocol version 2 patients receiving ACEi/ARBs at maximally tolerated labelled daily dose were eligible to enroll in the study, unless contraindicated. In Protocol version 3 patients in whom ACEi/ARBs were not indicated were also eligible to enroll in the study. The applicant should explain the effect of these protocol changes on the study population given that patients who are not indicated to take ACEi or ARB might have milder disease than patients who are on therapy.

Exclusion criteria were applied to reduce the potential for bardoxolone-induced fluid overload identified in the large BEACON study (Study 0903) recruiting patients with T2DM and with Stage 4 CKD (eGFR ≥ 15 to < 30 mL/min/1.73 m^2). Therefore, both phases of Study 1603 excluded patients with eGFR <30 mL/min/1.73 m2, patients with a history of left-sided heart disease (including all subjects with New York Heart Association [NYHA] >II), and patients who had evidence of volume overload at baseline, defined as B-type brain natriuretic peptide (BNP) level of >200 pg/mL.

Subjects with NYHA III-IV were excluded from the pivotal study to reduce the potential for fluid overload; however, the applicant proposes a contraindication for subjects with NYHA IV only.

Subjects with CKD 4-5 (eGFR <30 mL/min/1.73 m2) were excluded from Study 1603 for safety reasons; however, the proposed indication includes all stages of renal function. No justification has been provided for the safe use in subjects with CKD 4-5 (eGFR <30 mL/min/1.73 m2) in Alport syndrome. Furthermore, medicinal products intended to prevent development or slow progression of chronic renal insufficiency generally tend to be less effective in subjects with severe compared to mild-moderate renal dysfunction due to increasing irreversible damage to the renal parenchyma, e.g., fibrosis and atrophy. Extrapolation of efficacy data from the study population therefore needs to be justified. In this context it is noted that in the subgroup analysis (see Results, subheading *Outcomes and estimation*), subjects with baseline eGFR ≤60 mL/min/1.73 m2 showed poorer results compared to subjects with baseline eGFR >60 mL/min/1.73 m2.
The applicant is requested to justify the use of bardoxolone in subjects with severe renal disease corresponding to CKD 4-5 (eGFR <30 mL/min/1.73 m2), taking both safety and efficacy into consideration, or to reflect the limitations of the study population in the wording of the indication.

Treatments

Development of bardoxolone methyl capsules began with a crystalline formulation. However, owing to low bioavailability, an amorphous SDD formulation was developed. Study 1603 Phase 2/3 was performed with the amorphous SDD of bardoxolone methyl which is also the intended commercial product.

Capsules containing bardoxolone methyl (5 mg or 15 mg strength) or matching placebo without the active ingredient were used in this study.

Adult patients (≥18 years of age) receiving bardoxolone methyl started with once-daily dosing at 5 mg with dose escalation to 20 mg at Week 4 (baseline UACR ≤300 mg/g), and then further to 30 mg at Week 6 (only if baseline UACR >300 mg/g). In both 1603/Phase 2 and 1603/Phase 3, treatment duration was 104 weeks with an off-treatment period Week 48-52 and Week 100-104.

Patients under the age of 18 years receiving bardoxolone methyl started dosing at 5 mg every other day during the first week and began once-daily dosing with 5 mg during the second week of the study. Thereafter, the same dosing as for adults were applied.

The dose-titration approach was applied to minimise potential tolerability issues. The dose could be reduced stepwise to a minimum of 5 mg or be temporarily discontinued if adverse events occurred.

Monitoring of liver enzymes and weight is considered warranted. This is reflected in the SmPC. Some rewording is however considered necessary.

The dosing schedule proposed for marketing is more gradual compared to the dosing schedule tested in Phase 2/3 trial. The dosing schedule proposed for marketing has not been tested in any clinical trial in the intended indication. The applicant should discuss and justify the proposed dosing schedule including reasons and data underpinning the more gradual dosing scheme proposed for marketing compared to dosing in both Phase 2/3 trial.

Outcomes/endpoints

Table 10: Summary of Efficacy Endpoints Study 1603 **Phase 3**

	Year 1	**Year 2**
Primary Endpoint	Change from baseline at Week 48 in eGFR (on treatment)	Change from baseline to Week 100 in eGFR (on treatment)
Key Secondary Endpoint	Change from baseline at Week 52 in eGFR (off treatment)	Change from baseline to Week 104 in eGFR (off treatment)
Exploratory Endpoints[a]		
Kidney failure composite[b]	N/A	Time to event analysis
Categorical changes in eGFR	• Percentage of patients with ⩾30% increase by Week 48 • Percentage of patients with ⩾30% decrease by Week 48	• Percentage of patients with ⩾30% increase by Week 100 • Percentage of patients with ⩾30% decrease by Week 100
Distribution of eGFR change (assessed as quartile changes)	Change from baseline at Week 48 and 52	Change from baseline to Week 100 and 104
Patient's Global Impression of Change	N/A	Week 100
Post-hoc Analysis	Annualized off-treatment eGFR slope	

Abbreviations: eGFR=estimated glomerular filtration rate; PGIC= Patient's Global Impression of Change
[a] Includes only endpoints discussed in the Clinical Overview of Efficacy. For discussion of additional exploratory endpoints, see the Study 1603 Phase 3 CSR.
[b] Defined as the occurrence of any one or more of the following events: 30% decline from baseline in eGFR, GFR <15 mL/min/1.73 m2, or ESKD (initiation of maintenance dialysis or kidney transplant).

The amendment of an additional primary endpoint at Week 100 is considered to meet the CHMP's comment (EMA/CHMP/SAWP/599796/2018) that analysis at Week 48 was too early and may therefore overestimate the effect of the product.

Study protocol version 3 (30 July 2018) introduced the time-to-first kidney failure outcome event as a composite exploratory endpoint.
Kidney failure composite outcome includes individual components of unequal clinical significance (ESRD, eGFR <15 mL/min/1,73 m2 and 30% decline from baseline in eGFR). According to the Guideline on the clinical investigation of medicinal products to prevent development/slow progression of chronic renal insufficiency (EMA/CHMP/500825/2016), renal failure is defined as CKD stage 5 (eGFR

<15 ml/min/1.73m2) or 5D (CKD with chronic dialysis treatment). Confirmed decline of 30% in eGFR does not indicate renal failure unless stage 5 or 5D is present at the same time. The applicant is asked to explain clinical significance behind decline of 30% in eGFR as one of the outcome components in the composite kidney failure outcome, especially considering very broad baseline eGFRs in study population.

The efficacy endpoints in 1603/Phase 2 were:

- Primary Efficacy Endpoint
    - Change from Baseline in eGFR at Week 12
- Secondary Efficacy Endpoints
    - Change from Baseline in eGFR at Week 48 and Week 100
- Exploratory Efficacy Endpoints
    - Change from baseline in eGFR at Week 52 and Week 104

In both phases, estimated glomerular filtration rate (eGFR) values based on creatinine were calculated at the central laboratory and used in data analyses. For patients consented at age 18 years and older, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used. For patients consented at age 12 to 17, the Bedside Schwartz equation was used.
Both equations are well established and widely used, and in line with recommendations for clinical studies (EMA/CHMP/500825/2016).

In protocol assistance (EMA/CHMP/SAWP/599796/2018), the CHMP recommended that the primary efficacy endpoint should be timed to a predefined and justified loss in GFR, such as 50%.
The applicant has commented that the choice of primary endpoint as "change in eGFR from baseline over 2 years duration" is conceptually consistent with the importance of total eGFR slope highlighted in NKF sponsored workshop conducted in collaboration with the FDA and EMA in March 2018 with conclusions published in January 2020 (Levey, 2020). This is agreed.

These end points are less applicable at higher baseline GFR and in the context of agents that cause an "acute effect" on GFR decline (i.e., an early treatment effect of the intervention that differs from the later treatment effect), making them less practical for drugs targeted at earlier stages of kidney disease and drugs with potential hemodynamic effects. Surmounting these limitations may involve examining changes in albuminuria (or proteinuria) as an earlier marker of kidney disease progression, assessing the rate of GFR decline (slope), and combined use of both these approaches. In Study 1603 Phase 2/3, assessment of the slope of eGFR decline beyond Week 48 is however not possible due to the two off-treatment periods Week 48-52 and Week 100-104.

Justification of Off-Treatment Efficacy Endpoint

To address the concern that the treatment effect was due an increase in intraglomerular pressure which would be detrimental for disease progress the applicant has included the two four-week off treatment periods after W48 and W100 respectively. According to the applicant, non-clinical data indicate that bardoxolone methyl produces acute increases in eGFR by increasing glomerular surface area and by reversing endothelial dysfunction and mesangial cell contraction, restoring GFR of individual nephrons without changes in intraglomerular pressure (pending responses to the LoQ where additional clarifications are requested), but these data need clinical confirmation. Therefore, the off-treatment periods were added to the protocol. To confirm that the optimal off-treatment duration was beyond the timeframe for resolution of acute PD effects the applicant presented the following justification:

- The terminal half-life of bardoxolone is estimated to be approximately 48 h. Thereby, bardoxolone methyl concentrations in plasma decrease to sub-pharmacologic concentrations in approximately 2 weeks.
- A population-based exposure-response modelling demonstrating that the increase in eGFR after oral administration is proportional (direct relationship) to bardoxolone methyl concentrations in plasma. As discussed in the section 2.2.7 in Pharmacokinetic AR there are nevertheless limitations to this model and the assumption that effect would increase and decrease at the same rate is not justified.
- The two studies with treatment duration ≤8 weeks mean eGFR had returned to baseline four weeks post-treatment. In the absence of chronic impact on the renal function due to the short study duration, this should be attributed to acute PD effects.
- Serial off-treatment eGFR data are available from patients who were treated with bardoxolone methyl (n=15) and had off-treatment eGFR values collected up to 42 days post-dose. Analyses of serial off-treatment eGFR values in these patients demonstrate that in resolution of acute PD effect from bardoxolone methyl, the declination in eGFR is largest during the first seven days post-dose. The data are limited and variable hampering the possibility to draw firm conclusions, but the acute PD effects appears to be resolved within 28 days.
- Analyses using all off-treatment eGFR values in the ISS dataset (n=1094 observations from 652 patients) collected between 1 to 42 days after last dose from all completed bardoxolone methyl trials that were not terminated prematurely indicate a return to baseline within four weeks. These data are, however, highly variable, and should be interpreted with caution.
- Measured GFR data, as assessed with inulin clearance, indicated complete resolution of acute PD effects within 4 weeks after last dose in the placebo-controlled Study 005, enrolling subjects with diabetes.
- Data indicating a normalisation of ALT, AST and GGT four weeks after study drug withdrawal was provided from Study 1603 and a cohort of three placebo-controlled studies (Studies 005, 0903 and 1603). It is however uncertain whether the resolution of these PD variables follows the same timeline as the acute PD effects on eGFR.

In summary, the data supporting the 30-day-window is limited and with high variable quality. There are however indications that the 30 days off-treatment may not be sufficient for a complete washout of pharmacodynamic effects. Please refer also to the Results-section, subheading *Outcomes and estimation.* Of note, the visit window for the Week 52 and Week 104 analyses was broad, allowing test sampling after as little as two weeks off treatment. The purpose of the analysis of the secondary endpoints based on week 52 and week 104 data was to examine any remaining effect after 4 weeks of treatment discontinuation. Hence, a supplementary analysis should be performed on observed values without imputation including only values at least 4 weeks after last dose of study treatment.

Sample size

Study 1603/Phase 3: With 150 patients enrolled (75 in each group), the study would have approximately 80% power to detect a difference between the two treatment groups in change from baseline in eGFR of 3.1 mL/min/1.73 m2 for the primary endpoint (i.e., Week 48 in Year 1 or Week 100 in Year 2). The power calculation, which was based on mixed-model repeated measures (MMRM) analysis, assumed the following: 9 repeated measurements having compound symmetry covariance structure; The correlation between observations on the same subject is 0.7; Two-sided Type I error

rate of 0.05; Standard deviation of change from baseline in eGFR of 8 mL/min/1.73 m2; Analyses based on the intent-to-treat (ITT) population.

The sample size calculation for the 1603/phase 3 study was based on a Type I error rate of 0.05. The actual analysis was adjusted for multiple testing. In protocol version 2 the sample size was decreased from the originally planned 180 subjects to 150. The reason was use of MMRM method instead of t-test in the calculation.

Study 1603/Phase 2: With 30 patients, the Study had over 80% power to detect a change from baseline in eGFR relative to zero (no change). The power calculation assumed the following: Two-sided type I error rate of 0.05; 5% of the patients will not complete the full course of study treatment; A mean change from baseline in eGFR of 4.3 mL/min/1.73 m2 (on treatment); An SD of change from baseline in eGFR of 8 mL/min/1.73 m2 (on treatment).

Randomisation and blinding (masking)

An Interactive Web Response System (IWRS) was used to randomize Study 1603/Phase 3 patients 1:1 to bardoxolone methyl or placebo. Randomization was stratified by screening UACR using the following categories: UACR ≤300 mg/g, UACR >300 mg/g to ≤1000 mg/g, UACR >1000 mg/g.

Randomisation and stratification are generally endorsed, although adding a stratum of UACR <30 mg/g would have been informative when it comes to making a balance between treatment arms regarding disease progression/severity. The applicant should present the number and percentage of subjects with UACR <30 mg/g per treatment arm and should present subgroup analyses for the primary efficacy outcome for these patients.

For the double-blind Study 1603/Phase 3, all patients, investigators, site personnel, laboratories, and central readers with direct involvement in the conduct of the study or their designees were blinded to treatment assignments. To maintain the blind, investigators distributed blinded study drug treatment kits to patients as directed by the IWRS system. Investigators and patients were not blinded to dose level but were blinded to treatment assignment.

This 2-year study included an option for final analysis of Year 1 endpoints while the second year of the trial was ongoing. This design was intended to allow the new drug application (NDA) process to be initiated early if Year 1 data were clearly positive.

The Study 1603/Phase 3 Year 1 efficacy endpoints were analysed after all patients in Study 1603/Phase 3 completed their Week 52 visit. The Year 2 efficacy endpoints were analysed after all patients completed their Week 104 visit. A Data Access Plan was implemented, which described the planned sequence of events for the analysis of Year 1 data and prospectively described procedures to limit, control, and document access to unblinded data through the duration of the trial. The purpose of the Data Access Plan was to maintain the integrity of the trial data until the last patient completed the last Year 2 visit.

In protocol version 4 (22 April 2019), very late during the trial, the applicant separated Year 1 from Year 2 endpoints. Year 1 endpoint design was changed from time-to-event analysis to assessment of the percentage of bardoxolone methyl-treated patients relative to placebo with a kidney failure event. Year 2 endpoint remained as time-to-event analysis.

Separation of endpoints following the first year of treatment from endpoints following the second year of treatment seems to be implemented with the intention of the Sponsor to pursue regulatory approval in the USA after completion of the first year of treatment. The original Data Access Plan was dated 15 August 2019. Bearing in mind that all 157 participating patients were randomised between August 2017 and November 2018, it follows that all patients were receiving treatment with bardoxolone or

placebo for at least several months before the possibility of unblinding was introduced. The applicant should clarify what data was used (e.g., whether the data was on patient or aggregate level, blinded or unblinded, internal or external etc) to introduce the possibility of early unblinding well into the course of the trial (part of Study conduct MO).

The Data Access Plan describes three levels of access to unblinded data. The applicant should clearly state who was given access to each of these levels, at what time point, and their respective roles in the trial design, conduct and analyses in order to better assess the impact of the unblinding on study integrity.

From the submitted CARDINAL Phase 3 Data Monitoring Committee (DMC) meeting minutes, it is evident that premature unblinding of the study at Year 1 was discussed and was discouraged by the DMC (July, August, September 2019 meetings). This aforementioned issue and concerns about internal validity of the study consequently to Year 1 unblinding are discussed in *Conduct of the study* section and are part of the Study conduct MO.

The clinical database was locked 3 times during the trial. The clinical database was locked on 07 November 2019 and 09 December 2019 to allow for final analysis of the Year 1 endpoints while the second year of the trial was ongoing. The final database lock for the trial occurred on 06 November 2020. The randomization code to unblind the analysis team was provided after the database lock transfer. The SAP was finalized on 4 Nov 2019, prior to the first database lock.

Study 1603/Phase 2 was a single arm, non-randomised, open label study.

Statistical methods Study 1603/Phase 3

Analysis Populations

- Intent-to-treat population (ITT population): The ITT population is defined as all enrolled patients. Primary analyses of efficacy endpoints used the ITT population.
- Modified Intent-to-treat (mITT) population: "As-Treated" analysis of the ITT population that only includes eGFR values collected while receiving treatment.
- Year 1 Per-Protocol (PP) population: The Year 1 PP population is defined as patients who received study drug through Week 48 and had no protocol deviation that could potentially affect the efficacy conclusions. Review of protocol deviations for determining the Year 1 PP population was performed by a blinded team prior to Year 1 database lock.
- Year 2 PP population: The Year 2 PP population is defined as patients who received study drug through Week 100 and had no protocol deviation that could potentially affect the efficacy conclusions. Review of protocol deviations for determining the Year 2 PP population was performed by a blinded team prior to the final database lock.

Missing Data

Missing data were not imputed, unless otherwise specified. Any laboratory value (including eGFR), vital sign assessment, or ECG value collected after starting dialysis or after receiving a kidney transplant was considered invalid and were treated as missing. Additionally, summary tables and analyses did not include efficacy and safety data (clinical laboratory [including eGFR], vital sign, electrocardiogram, visual acuity, and audiology assessments) collected after the start date of adverse event preferred term "coronavirus".

The primary analysis of efficacy was based on an assumption of missing at random (MAR). The tipping point sensitivity analysis was performed to assess how severe departures from MAR must be in order

to overturn conclusions from the primary analysis. Missing eGFR data were not imputed for the primary MMRM analysis of the primary endpoints (Week 48 and Week 100). Missing eGFR data were imputed for the primary ANCOVA analysis of the key secondary endpoints (Week 52 and Week 104) using multiple imputation based on an assumption of MAR.

In the primary and secondary analyses, eGFR collected after starting dialysis or after receiving a kidney transplant is considered invalid and is treated as missing and the primary analysis of efficacy is based on an assumption of missing at random (MAR). This approach is not accepted. Starting dialysis or receiving a kidney transplant is an indication of a permanently failed kidney function and values after such event should be imputed with a worst possible score. Hence, all primary and secondary analyses should be repeated where observations after starting dialysis or after receiving a kidney transplant is imputed with a worst possible score (e.g., 5 mL/min/1.73m^2).

Also, values collected after the start date of adverse event preferred term "coronavirus" has been excluded from analysis. Although an assumption of MAR is more plausible in this case, a sensitivity analysis including all such values should be provided for primary and key secondary endpoints.

Type I error control

The trial included separate Phase 2 and Phase 3 cohorts, where the cohorts constitute independent sets of patients. Therefore, the Phase 2 analysis had no impact on the Type I error rate for the Phase 3 analysis.

The 1603/Phase 3 cohort included a family of hypothesis tests following the first year of treatment and a second family of hypothesis tests following the second year of treatment. All endpoints tested at Year 1 used a significance level of 0.025 and those tested at Year 2 used a significance level of 0.025. Within each year, endpoints were tested following a fixed-sequence hierarchical testing strategy.

Testing endpoints in the following sequence protects the overall type I error rate of 0.05 for the study:

Year 1 Testing Sequence (all significance levels = 0.025).

1. eGFR at Week 48 (primary at Year 1)
2. eGFR at Week 52 (key secondary at Year 1)

Year 2 Testing Sequence (all significance levels = 0.025):

1. eGFR at Week 100 (primary at Year 2)
2. eGFR at Week 104 (key secondary at Year 2)
3. time-to first kidney failure composite (exploratory at Year 2)
4. distribution of PGIC at Week 100
5. distribution of CGI-I at Week 100

All remaining endpoints were considered "Exploratory" and presented with nominal significance levels for descriptive purposes only.

The method to protect the overall type I error as presented above is considered acceptable. However, in the study report, it is stated that "*Because both Year 1 endpoints in the testing sequence were statistically significant at a level of 0.025, 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, the Year 2 testing sequence used a significance level of 0.05*." Although, this procedure per se could be acceptable, it was not prespecified in the protocol or SAP and hence is not accepted. Hence all p-values for year 2 testing should be interpreted against the prespecified alpha level of 0.025 and all confidence

intervals should be presented as 97.5%, both for primary analysis and sensitivity analyses. Furthermore, the tipping point analysis for year 2 should be repeated with the 0.025 level of significance.

Efficacy analysis of primary endpoints

The change from baseline eGFR for patients treated with bardoxolone methyl was compared with placebo at Week 48/Week 100 using mixed models repeated measures (MMRM) analysis, with baseline eGFR, baseline UACR strata, and fraction of 1-year/2-year exposure to treatment as covariates and the following fixed factors as covariates: treatment group, time (i.e., analysis visit number), the interaction between treatment and time, and the interaction between baseline eGFR and time. The Week 100 analysis also included geographical region (US vs. ex-US) as a covariate.

Analysis of eGFR at Week 48/Week 100 used all available eGFR values, irrespective of whether or not a patient was receiving treatment and missing data were not imputed.

An unstructured covariance matrix was used. The difference between bardoxolone methyl and placebo in change from baseline in eGFR was estimated along with the 97.5% confidence interval (CI) at Week 48/Week 100.

The inclusion of fraction of 1-year/2-year exposure to treatment as covariate in the primary analysis of the primary and secondary endpoints is not in line with the EMA Guideline EMA/CHMP/295050/2013 *Adjustment for baseline covariates in clinical trials* since it could be affected by the allocated treatment. As stated in the guideline. "*When a covariate is affected by the treatment either through direct causation or through association with another factor, the adjustment may hide or exaggerate the treatment effect*". Hence all analyses of primary and secondary endpoints should be repeated both including and excluding this covariate (both original analysis and analysis with imputations mentioned above).

Analysis of key secondary endpoints

The change from baseline eGFR at Week 52/Week 104 (or 4 weeks after last dose for patients who discontinued early) for patients treated with bardoxolone methyl was compared with placebo using an analysis of covariance (ANCOVA) model, with baseline eGFR, and fraction of 1-year/2-year exposure to treatment as covariates and treatment group and randomized UACR strata as a fixed effect. The Week 104 analysis also included geographical region (US vs. ex-US) as a covariate. Missing Week 52/Week 104 eGFR data were imputed using treatment-based multiple imputation.

The difference between bardoxolone methyl and placebo in change from baseline of eGFR was estimated along with the 97.5% CI at Week 52.

Sensitivity analyses

Sensitivity analyses were included to assess the robustness of conclusions to the primary and key secondary efficacy endpoint (ie, change in eGFR at Week 48). The following sets of prespecified sensitivity analyses are summarized in tables and forest plots: tipping point with multiple imputation, control-based imputation, MMRM fit to the As-Treated population (mITT), and MMRM fit to the PP population. For the Year 2 primary efficacy endpoint a pre-COVID era and post-COVID era comparison analyzed using ANCOVA was also performed. All eGFR values collected 14 days or more after the last dose of study drug were excluded from the As-Treated analysis.

Statistical methods Study 1603/Phase 2

The ITT population was defined as all enrolled patients. Analysis of primary and secondary efficacy endpoints was based on the ITT population.

The primary efficacy variable was the change from baseline in eGFR after 12 weeks of treatment, missing data were not imputed. A mixed-model for repeated measures (MMRM) was used to analyse the primary efficacy endpoint. Change from baseline in eGFR was calculated for each scheduled visit after Day 1 through Week 12 visit (ie, Weeks 1, 2, 4, 6, 8, and 12). The primary inference was the test of least squares (LS) mean at each timepoint relative to zero. Missing eGFR values were not imputed for the primary analysis of efficacy. Only on-treatment data were included in the primary analysis.

Whether eGFR collected after starting dialysis or after receiving a kidney transplant was included in the analysis is not clear and should be clarified. If such values were excluded from analysis, new analysis with a worst-case imputation should be provided.

RESULTS

Participant flow

Table 11: Disposition of Patients (Safety Population) (Study 1603 Phase 3*)*

Description of Patients	Placebo (n=80) n (%)	Bardoxolone Methyl (n=77) n (%)
Safety Population	80 (100)	77 (100)
ITT Population	80 (100)	77 (100)
Year 1		
Year 1 Per-Protocol Population	66 (82.5)	53 (68.8)
On Treatment at Week 48	71 (88.8)	60 (77.9)
Discontinued Study Treatment Prior to Week 48	9 (11.3)	17 (22.1)
Reason for Discontinuing Treatment		
Adverse Event	4 (5.0)	8 (10.4)
Withdrawal by Subject	3 (3.8)	2 (2.6)
Protocol-Specified Withdrawal Criterion Met	0	6 (7.8)
Lost to Follow-Up	1 (1.3)	1 (1.3)
Other	1 (1.3)	0
Completed Treatment Through Week 48 and had a Week 52 Study Visit	71 (88.8)	60 (77.9)
Year 2		
Year 2 PP Population	62 (77.5)	47 (61.0)
Received at least one dose in Year 2	69 (86.3)	58 (75.3)
On Treatment at Week 100	67 (83.8)	51 (66.2)
Discontinued Study Treatment in Year 2 Prior to Week 100	2 (2.5)	7 (9.1)
Reason for Discontinuing Treatment		
Adverse Event	0	1 (1.3)
Withdrawal by Subject	2 (2.5)	2 (2.6)
Protocol-Specified Withdrawal Criterion Met	0	1 (1.3)
Pregnancy	0	1 (1.3)
Lost to Follow-Up	0	1 (1.3)
Other	0	1 (1.3)
Completed Treatment Through Week 100 and had a Week 104 Study Visit	67 (83.8)	51 (66.2)
Completed Study Follow-up Through Week 104	79 (98.8)	75 (97.4)

Between August 2017 and November 2018, 371 subjects were screened, of which a very large number were excluded (n=214). The vast majority of excluded subjects failed to meet inclusion criteria (184 subjects). Hence, the generalisability of the study results is questionable based on the fact that over

50% of potentially eligible patients were not suitable for inclusion in this single pivotal trial. The applicant is invited to discuss generalisability in face of these exclusions.

The majority of subjects completed the 1603/Phase 3 study follow up through Week 104 (Placebo 99%; bardoxolone 97%). However, only 51/77 subjects (66%) in the bardoxolone arm versus 67/80 (84%) subjects in the placebo arm completed treatment through Week 100 and had a Week 104 study visit.
The difference between the treatment arms was driven primarily by more discontinuations in Year 1 of the study due to protocol-specified withdrawal criteria (6 [7.8%] in the bardoxolone methyl group and none in the placebo group) and AEs (8 [10.4%] in the bardoxolone methyl group and 4 [5.0%] in the placebo group). The applicant is asked to clarify which protocol-specified withdrawal criteria lead to discontinuation.

Furthermore, the applicant should present discontinuations over time in the form of Kaplan-Meier curves for each treatment arm, for both discontinuation of treatment and discontinuation of study**.**

A pronounced imbalance in discontinuations between the two treatment arms can potentially bias the results. For exploratory purposes, observed data only can be reviewed. These analyses do not look favourable for bardoxolone (please refer to the *Results section - Outcomes and estimation).*

In 1603/Phase 2, all subjects were still on treatment at the primary analysis at Week 12. At Week 104, 7/30 (23%) had discontinued study treatment. 24/30 (80%) of the subjects completed the 1603/Phase 2.

Treatment compliance

In Study 1603/Phase 3 in Year 1, 76/80 (95%) placebo patients and 63/77 (82%) bardoxolone methyl patients were dispensed study drug through Week 36 (last drug dispensation visits in Year 1), and in Year 2, 67/80 (84%) placebo patients and 50/77 (65%) bardoxolone methyl patients were dispensed study drug at the Week 88 visit (last drug dispensation visits in Year 2). Although the applicant claims that the number of patients with ≥80% compliance with study medication is above 90% in both groups, there is evident imbalance between groups driven by more bardoxolone patients having lower treatment compliance according to last dispensation visits in both year 1 and 2.

Recruitment

Date first patient consented: 15 February 2017 (1603/Phase 2), 24 July 2017 (1603/Phase 3)

Date last patient completed: 19 July 2019 (1603/Phase 2), 30 October 2020 (1603/Phase 3).

1603/Phase 2 of the study was conducted at 16 sites in the United States.
1603/Phase 3 was conducted at 57 sites in the United States, Australia, France, Germany, Japan, Spain, and United Kingdom, of which 48 sites randomized patients into the study

Conduct of the study

<u>Protocol amendments 1603/Study 1603</u>

The first protocol (version 1.0) was signed 15 November 2016. Major amendments during the study are given below.

- Version 2.0 (03 August 2017)
    - Added change from baseline in eGFR at Week 52 as exploratory endpoint for Phase 2
    - Added global impressions of change scores as exploratory endpoints

    - Removed interim analysis of efficacy from Phase 3 portion of study
    - Sample size in Phase 2 changed from "up to 30" to "approximately 30" and in Phase 3 from "up to 180" to "approximately 150"
    - Updated to reflect smaller numbers of macroalbuminuria patients available for the study
- Version 3.0 (30 July 2017)
    - Added time-to- kidney failure as an exploratory endpoint
    - Maximum age increased from 60 to 70
    - Added change from baseline in eGFR relative to placebo at Week 52 fas key secondary endpoint in Phase 3.
- Version 4.0 (22 April 2019)
    - Added analysis of renal failure composite endpoint as a Year 1 objective
    - Specified Week 100 eGFR and safety as Year 2 primary endpoint for Phase 3.
    - Specified eGFR at Week 104 as the Year 2 secondary objective for Phase 3.

In the third amendment (Version 4.0), an additional primary endpoint (eGFR at Week 100) was introduced. This was to meet the comment from EMA in the protocol assistance procedure, that the timing of the proposed primary endpoint of change in eGFR from baseline to Week 48 is too early and carries a risk of overestimating the benefit of the compound. This is endorsed.

However, extensive protocol changes generate challenges to data analysis and interpretation, especially because many of them occurred part way through the trial. The final version of the protocol (version 4) was dated approximately 5 months after the last patient was entered into the study. The volume, nature and timing of protocol changes raise concerns regarding study integrity. The applicant should clarify if any of the protocol changes occurred as a result of unscheduled and/or unblinded analyses. Any potential impact on the Type 1-error should be discussed.

The overall frequency of major protocol deviations is considerable (48.8% in placebo and 54.5% in bardoxolone), which is concerning. Deficiencies in informed consent, procedures, and inclusion/exclusion criteria were most frequent. Most patients (81/157, 52%) had at least one major protocol deviation.

Major protocol deviations regarding informed consent were recorded in 18/80 patients from placebo group (22%) and 17/77 patients from bardoxolone group (22%). These deviations included failure to re-consent a patient to a new version of the ICF in a timely manner or failure to consent to the correct ICF, completion of portions of the ICF by the PI that were meant to be completed by the patient, missing or incorrect information on a signed ICF, failure to sign a version of the ICF, and consent of patient to version that was not yet approved by the ethics committee. The applicant is asked to explain how these types of protocol deviations occurred and how they were handled. The applicant should inform if a pattern in these deviations was observed (ie. clustering in any particular study centre or at any particular timepoint). If any of these deviations led to subsequent permanent withdrawal of the informed consent should also be stated.

Major protocol deviations regarding study procedures were recorded in 17/80 patients from placebo group (21%) and 21/77 patients from bardoxolone group (27%). These deviations included failure of the patient to inform PI of weight gain and/or failure to have an unscheduled assessment following weight increase of 2.3 kg or greater and/or missed follow-up after elevated BNP or transaminases.

From a safety point of view, these types of protocol deviations are especially troubling and can have serious effects on patients' health as treatment with bardoxolone methyl can poses a risk for fluid overload. The applicant is asked to explain what steps were taken to ensure patient safety in these instances.

Of note, in both phases, a small number of subjects were included in the study on a waiver despite eGFR outside the broad eligibility criteria of 30-90 mL/min/1.73 m2. This has not been explained. The applicant is asked to clarify the use of a waiver to include subjects with eGFR outside the eligibility criteria.

Study 1603/Phase 2 and the first 76 weeks of 1603/Phase 3 were completed before the start of the COVID19 pandemic. After Week 76 in 1603/Phase 3, approx. 20% of all visits were impacted by COVID-19. More visits in the placebo arm compared to the bardoxolone arm were affected, e.g., 26% versus 21% of the visits at Week 100 (primary endpoint). Summary tables and analyses did not include efficacy and safety data (clinical laboratory [including eGFR], vital sign, electrocardiogram, visual acuity, and audiology assessments) collected after the start date of adverse event preferred term "coronavirus". A sensitivity analysis including all values for primary and key secondary endpoints is requested (please refer to subheading *Statistical methods* above).

From the submitted Study 1603 (CARDINAL) Phase 3 Data Monitoring Committee (DMC) meeting minutes, it is evident that unblinding of the Sponsor prematurely (at Year 1) was discussed and was discouraged by the DMC (July, August, September 2019 meetings). The DMC had concerns about analysing and publicising Year 1 results while the study was ongoing as it could compromise the integrity of Year 2 data and raise ethical questions about a) continuing patients on placebo if the results were positive, or b) continuing patients on study if the results were negative. The DMC advised that a written FDA approval of such analysis should be obtained prior to proceeding. The Sponsor decided to unblind themselves after finding out that the study met its primary endpoint at Year 1. However, all the concerns raised by the DMC remain and threaten the integrity of the pivotal trial. Sponsor unblinding was not foreseen in the Protocol and its amendments. The unblinding was foreseen by a Data Access Plan, which was introduced approximately 8 months after the last patient was randomised into the trial. The applicant should address these issues thoroughly.

Concerns regarding the internal validity of the pivotal trial are further emphasised based on DMC meeting minutes from November 27, 2019. The DMC met to discuss the public release of one-year study results and its implication to study participants and integrity of the trial. The DMC members "agreed they felt pressured by the sponsor to perform the one-year interim analysis and deliver not only the agreed upon results, but also to make a recommendation for stopping the trial early without prespecified stopping rules or without a safety concern. This pressure in part was exerted based upon the verbal representation that US FDA guidance to the Reata described to the DMC by the sponsor representative requested this interim assessment. The DMC was not provided with, and therefore did not review, any official communication from the FDA to the sponsor concerning the one-year analysis, public release of study results, or the pathway forward after the public was informed". The one-year study results were made public on November 11, 2019, and by the date of the DMC meeting (November 27), the Sponsor had not produced any of the plans or documents requested priorly by the DMC including re-consent documents for study participants, communication plan to study participants, investigators and Institutional Review Boards. The Sponsor argued that they did inform (via e-mail) the sites and instructed them to talk to participants regarding year 1 results and that the press release is to be forwarded to site's IRB. The Sponsor did not agree that a re-consent procedure is necessary. However, no written communication plan was provided. Although the DMC accepted the Sponsor's actions, they are viewed as ethically questionable. The applicant should discuss the impact of public release of results on the safety and well-being of participants already included in the trial and on study conduct. In addition, the applicant should clarify why re-consent was not needed.

From the submitted CARDINAL Phase 3 DMC meeting minutes it is evident that an issue including a site in Germany and the German regulatory authority (BfArM) arose (DMC meeting minutes: 13 September 2019 Ad hoc German Bfarm; 22 January 2020 Ad hoc Call to discuss German Site; M 5.3.5.1). The German PI was concerned that patients receiving bardoxolone show faster progression of kidney disease. As a response, an independent unblinded analyses of safety parameters for 5 patients included in Germany was performed. The analysis concluded that "There are no specific site or patient level concerns with respect to patient safety, risk-to-benefit relationship, or study integrity". No further actions were undertaken by the German regulatory authority. However, the participants from Germany discontinued their involvement in the study. Several questions regarding the issue of possible faster progression to ESRD are raised.

It appears that the final DMC meeting minutes are incomplete. Meeting minutes from the 14th DMC safety review held on September 1, 2020, state that "the next DMC meeting will occur on November 14 2020, and will include a review of the Year 2 results and proposed press release by the Sponsor". The DMC expressed a wish to debrief Reata on their experience as a DMC once the study has been completed unblinded'. At the same meeting, the DMC requested a series of additional analyses (observed eGFR values only) from the biostatistics team. The additional analyses were provided in the DMC meeting minutes, and generally look less favourable compared to the analyses presented in the CSR. However, other than unsigned meeting session summary for a meeting held on 8th November 2020, no meeting minutes for the meeting scheduled for November were provided. These are requested.

Baseline data

The baseline demographics for the 1603/Phase 3 cohort are summarised in Table 12 and baseline characteristics in Table 13

Table 12: Demographics (Safety Population) (Study 1603 Phase 3*)*

	Safety Population		**Pediatric Subpopulation (<18 Years)**	
	Placebo (N = 80)	**Bardoxolone Methyl (N = 77)**	**Placebo (N = 12)**	**Bardoxolone Methyl (N = 11)**
Age (years)				
Mean (SD)	39.6 (16.03)	38.8 (14.55)	15.2 (1.64)	15.4 (1.21)
Min, Max	13, 70	13, 65	13, 17	13, 17
Age <18 years, n (%)	12 (15.0)	11 (14.3)	12 (100)	11 (100)
Age ≥18 years, n (%)	68 (85.0)	66 (85.7)	0	0
Sex, n (%)				
Female	48 (60.0)	43 (55.8)	3 (25.0)	1 (9.1)
Male	32 (40.0)	34 (44.2)	9 (75.0)	10 (90.9)
Race, n (%)				
American Indian or Alaska Native	1 (1.3)	0	0	0
Asian	12 (15.0)	14 (18.2)	4 (33.3)	3 (27.3)
Black or African American	2 (2.5)	3 (3.9)	1 (8.3)	2 (18.2)

	Safety Population		Pediatric Subpopulation (<18 Years)	
	Placebo (N = 80)	**Bardoxolone Methyl (N = 77)**	**Placebo (N = 12)**	**Bardoxolone Methyl (N = 11)**
Native Hawaiian or Other Pacific Islander	0	1 (1.3)	0	0
White	63 (78.8)	55 (71.4)	5 (41.7)	4 (36.4)
Other	2 (2.5)	4 (5.2)	2 (16.7)	2 (18.2)
Ethnicity, n (%)				
Hispanic or Latino	10 (12.5)	9 (11.7)	1 (8.3)	3 (27.3)
Not Hispanic or Latino	70 (87.5)	68 (88.3)	11 (91.7)	8 (72.7)

Table 13: Baseline Characteristics (Safety Population) (Study 1603 Phase 3*)*

	Safety Population		Pediatric Subpopulation (<18 Years)	
	Placebo (N = 80)	**Bardoxolone Methyl (N = 77)**	**Placebo (N = 12)**	**Bardoxolone Methyl (N = 11)**
Baseline eGFR (mL/min/1.73 m^2)				
Mean (SD)	62.63 (18.234)	62.74 (17.719)	68.15 (16.229)	71.88 (14.954)
Min, Max	28.2, 91.3	29.5, 96.6	32.9, 84.9	36.9, 89.9
eGFR Category, n (%)				
≤60 mL/min/1.73 m^2	33 (41.3)	33 (42.9)	2 (16.7)	2 (18.2)
>60 mL/min/1.73 m^2	47 (58.8)	44 (57.1)	10 (83.3)	9 (81.8)
Baseline UACR (mg/g)				
Geometric mean (SE)	134.45 (33.366)	148.09 (34.262)	136.59 (89.974)	409.35 (187.045)
Min, Max	1.2, 3031.0	2.1, 3495.0	5.0, 2385.0	54.0, 2660.0
Baseline UACR ≤300 mg/g, n (%)	43 (53.8)	42 (54.5)	6 (50.0)	4 (36.4)
Baseline UACR >300 mg/g, n (%)	37 (46.3)	35 (45.5)	6 (50.0)	7 (63.6)
Baseline CKD Stage, n (%)				
1	2 (2.5)	1 (1.3)	0	0
2	46 (57.5)	43 (55.8)	10 (83.3)	9 (81.8)
3a	15 (18.8)	18 (23.4)	0	1 (9.1)
3b	15 (18.8)	14 (18.2)	2 (16.7)	1 (9.1)
4	2 (2.5)	1 (1.3)	0	0
Baseline Hematuria Present, n (%)	68 (85.0)	67 (87.0)	9 (75.0)	10 (90.9)

	Safety Population		Pediatric Subpopulation (<18 Years)	
	Placebo (N = 80)	**Bardoxolone Methyl (N = 77)**	**Placebo (N = 12)**	**Bardoxolone Methyl (N = 11)**
Hearing Loss (Yes), n (%)	34 (42.5)	36 (46.8)	6 (50.0)	5 (45.5)
Visual Impairment (Yes), n (%)	19 (23.8)	18 (23.4)	2 (16.7)	0
Age at Alport Syndrome Diagnosis (years)				
Mean (SD)	29.6 (18.79)	29.7 (16.97)	10.6 (5.85)	10.5 (4.32)
Min, Max	1, 70	3, 62	2, 17	3, 16
Histological Diagnosis (Yes), n (%)	15 (18.8)	17 (22.1)	3 (25.0)	3 (27.3)
Genetic Diagnosis, n (%)				
XLAS Subtype	51 (63.8)	47 (61.0)	8 (66.7)	6 (54.5)
Non-XLAS Subtype	24 (30.0)	24 (31.2)	3 (25.0)	3 (27.3)
Mutation, n (%)				
COL4A3 Mutation	7 (8.8)	7 (9.1)	0	2 (18.2)
COL4A4 Mutation	13 (16.3)	17 (22.1)	2 (16.7)	1 (9.1)
COL4A4 and *COL4A3* Mutation	4 (5.0)	0	1 (8.3)	0
COL4A5 Mutation	51 (63.8)	47 (61.0)	8 (66.7)	6 (54.5)
COL4A5 and *COL4A3*	1 (1.3)	0	0	0
COL4A5 and *COL4A4*	0	1 (1.3)	0	0
ACEi/ARB Use (Yes), n (%)	60 (75.0)	62 (80.5)	8 (66.7)	9 (81.8)
BMI (kg/m^2)				
Mean (SD)	26.223 (6.0782)	26.962 (5.7058)	20.388 (3.5325)	21.954 (2.1116)
Min, Max	15.95, 45.73	18.65, 41.11	15.95, 25.70	19.21, 25.02

Abbreviations: ACEi=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker; BMI=body mass index; CKD=chronic kidney disease; *COL4A3*=collagen type IV alpha 3 chain gene; *COL4A4*=collagen type IV alpha 4 chain gene; *COL4A5*=collagen type IV alpha 5 chain gene; eGFR=estimated glomerular filtration rate; Max=maximum; Min=minimum; SD=standard deviation; SE=standard error; UACR=urinary albumin-to-creatinine ratio; XLAS=X-linked Alport syndrome

The baseline demographics for the 1603/Phase 2 cohort are summarised in Table 14 and baseline characteristics in Table 15

Table 14: Demographics – Safety Population (Study 1603 Phase 2*)*

Parameter **Statistic**	**Bardoxolone Methyl** **(N = 30)**
Age (years)	
Mean (SD)	43.63 (12.557)
Min, max	14.0, 59.0
Age group, n (%)	
<18 years	2 (6.7)
≥18 years	28 (93.3)
Sex, n (%)	
Female	18 (60.0)
Male	12 (40.0)
Race, n (%)	
Asian	1 (3.3)
Black or African American	3 (10.0)
White	26 (86.7)
Ethnicity	
Hispanic or Latino	3 (10.0)
Not Hispanic or Latino	27 (90.0)

Table 15: Baseline Characteristics – Safety Population (Study 1603 Phase 2*)*

Parameter **Statistic**	**Bardoxolone Methyl** **(N = 30)**
Baseline BMI (kg/m^2)	
Mean (SD)	29.57 (6.822)
Min, max	18.8, 44.2
Baseline UACR group, n (%)	
≤300 mg/g	18 (60.0)
301 to 1000 mg/g	7 (23.3)
>1000 mg/g	5 (16.7)
Baseline eGFR (mL/min/1.73 m^2)	
Mean (SD)	54.17 (24.075)
Min, max	27.6, 94.0
Baseline eGFR group, n (%)	
≤60 (mL/min/1.73 m^2)	18 (60.0)
>60 (mL/min/1.73 m^2)	12 (40.0)
Age of Alport syndrome diagnosis (years)	
Mean (SD)	29.3 (19.61)
Min, max	2, 59
Genetic confirmation, n (%)	
No	1 (3.3)
Yes	29 (96.7)
Mode of inheritance, n (%)	
X-linked	21 (70.0)
Autosomal (recessive or dominant)	6 (20.0)
Unknown	2 (6.7)
Not applicable	1 (3.3)
Genotype, n (%)	
COL4A3	1 (3.3)
COL4A4	5 (16.7)
COL4A4, *COL4A5*	2 (6.7)
COL4A5	21 (70.0)
Not applicable	1 (3.3)
Confirmed histologic diagnosis, n (%)	
No	27 (90.0)
Yes	3 (10.0)
Baseline ACEi/ARB status	
ACEi	
No	17 (56.7)
Yes	13 (43.3)
ARB	
No	17 (56.7)
Yes	13 (43.3)
Both ACEi and ARB	1 (3.3)
Neither	5 (16.7)

Abbreviations: ACEi=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; BMI=bodymass index; eGFR=estimated glomerular filtration rate; max=maximum; min=minimum; SD=standard deviation; UACR=urine albumin-to-creatinine ratio

At study entry in the 1603/Phase 3 study, patients had progressively declining kidney function based on available historical eGFR values over the 5 previous years. The mean rate of decline for the overall pre-treatment ITT population (N = 128) was -5.1 (Placebo -4.9, bardoxolone -5.3) mL/min/1.73 m^2. In the 1603/Phase 2 cohort, the study patients' kidney function was declining at an average annual rate of -4.8 mL/min/1.73 m^2) prior to study entry.

Age and baseline eGFR are important prognostic factors in Alport's syndrome. In 1603/Phase 3, mean age and mean baseline eGFR were balanced between the treatment arms (39.6 versus 38.8 years and 62.6 versus 62.7 mL/min/1.73 m2 for placebo and bardoxolone, respectively). A similar proportion of the subjects in each treatment arm had the X-linked form of Alport's syndrome, associated with the COL4A5-mutation, which is the most common form of Alport, (51/80 [63.8%] in the placebo arm vs 47 [61.0%] in the bardoxolone arm).
Taken together, there were no major imbalances between the two treatment arms expected to have impact on study outcome.

There was a low proportion of EU participants (4.3%), but most of them were White (75%), and the applicant is claiming similar medical care in different regions. This can be acceptable provided that the applicant adequately address the issue of representativeness of EU population. The applicant is invited to elaborate whether Alport syndrome study population is representative of the EU-population taking possible differences in medical practices into consideration too (please refer to the ICH E5 and Reflection paper CHMP/EWP/692702/08).

Among paediatric participants, the vast majority were males (85.7%), which can be explained by X-linked variant of Alport syndrome. There was no paediatric participant included from the EU. A smaller proportion was White (47.6%) compared to overall population (75%). The applicant is invited to elaborate whether the Alport syndrome paediatric study population could be extrapolated the EU-population (please refer to the ICH E5 and Reflection paper CHMP/EWP/692702/08).

There seems to be discrepancies in baseline characteristics between the paediatric and the overall population since some indicators show worse renal function (UACR, UACR >300mg, haematuria at baseline), but others show better renal function (eGFR, CKD stage, ACE-inh/ ARB use). The applicant is asked to discuss those discrepancies in baseline renal function indicators among paediatric population enrolled in Alport syndrome safety pool, and in comparison to the overall population. It is questioned whether the paediatric patients enrolled were representative of younger Alport syndrome population as younger patients with Alport syndrome are at greater risk of CKD and progression. Although is acknowledged that the course can be more indolent with delayed kidney failure.

As the inclusion criteria do not define the lower threshold of baseline UACR (i.e., patients with a normal UACR value of <30 mg/g could be enrolled), it is important to establish that the bardoxolone and placebo group did not differ substantially in the distribution of baseline UACR values. In addition to already presented data (Table 14 in the CSR), the applicant is asked to present the categorical distribution of baseline UACR values in the following categories: <30 mg/g; ≥30 and <300 mg/g; ≥300 mg/g in both treatment arms. Additionally, the median values of baseline UACR should be reported for both treatment arms.

In regard to baseline ACEi/ARB status, 25% of patients in the placebo group and 20% of patients in the bardoxolone methyl group were not taking either of these medications. Patients who are not indicated to take ACEi or ARB might have milder disease than patients who are on therapy. The applicant should provide information on reasons for these patients not being on ACEi or ARB therapy and include the information on baseline eGFR, proteinuria and haematuria for these patients.

Adolescent subpopulation was well balanced between treatment arms with respect to baseline eGFR values with most of the subjects (10/12 in placebo group and 9/11 in bardoxolone methyl group) in

>60mL/min/1,73m2 category. However, regarding baseline UACR, subjects in bardoxolone methyl group had disproportionally higher geometric mean UACR values vs placebo (bardoxolone methyl group: 409; SE 187 vs placebo: 137; SE 90) which can indicate that there were discrepancies between groups when it comes to disease progression. The applicant is asked to comment on these differences.

Patients in the placebo group more frequently reported immune system disorders, musculoskeletal and connective tissue disorders, respiratory, thoracic and mediastinal disorders, and social circumstances disorders in their medical history compared to bardoxolone group patients. Bardoxolone group patients more frequently reported ear and labyrinth disorders and vascular disorders compared to placebo group. It appears that patients in placebo group had higher burden of concomitant diseases than patients in bardoxolone group. The applicant is asked to discuss whether these imbalances could have affected study outcomes.

The applicant seeks approval for the adolescent population based on the Phase 3 trial, in which 11 patients younger than 18 years of age were administered bardoxolone. With the additional 2 patients from the Phase 2 study, the combined pool of patients younger than 18 years of age who were studied in the pivotal trial of Alport syndrome indication is only 13. Even for an orphan indication, this is a very limited number.

At the time of the Scientific Advice/Protocol assistance, due to the safety profile which included incompletely understood gastrointestinal and cardiovascular adverse events, the CHMP advised against including adolescents into the CARDINAL study or administering bardoxolone to adolescents. The applicant was reminded that safety measures to determine the effect of bardoxolone on growth and development, including sexual development, are not detailed. The combined pool of patients younger than 18 years who were studied in the pivotal trial of Alport syndrome indication and were administered bardoxolone is very limited (11 patients in pivotal phase 3, and 2 patients in phase 2 of study 1603). A question regarding safety in the paediatric population is raised in the Safety part.

The eligibility criteria with regard to renal function were wide (baseline eGFR 30-90 mL/min/1.73 m^2 and UACR <3500 mg/g), and all three subtypes of Alport syndrome were eligible for inclusion. Even though there were no relevant differences between the treatment arms with regards to renal function and proportion of subjects with X-linked versus non-X-linked Alport syndrome, there is a marked heterogenicity within the treatment arms. In this context, the lifetime risk of ESRD with gender and different Alport subtype (Table 16) is of interest. In summary, the study population spans from subjects with baseline eGFR of 30 mL/min/1.73 m^2 and a disease subtype with 100% lifetime risk of ESRD to subjects with 90 mL/min/1.73 m^2 and a disease subtype with 20% lifetime risk of ESRD. Notwithstanding, the point estimate favoured bardoxolone for all prespecified subgroups (see subheading *Outcomes and estimates* below).

Table 16: Genetic Variants of Alport Syndrome and Risk of End-Stage Kidney Disease

Mode of Inheritance	Mutation	Sex	Risk of ESKD
X-linked (XLAS)	*COL4A5*	Male Female	100% 25%
Autosomal recessive (ARAS)	Both copies of either *COL4A3* or *COL4A4*	Male and Female	100%
Autosomal dominant (ADAS)	One copy of *COL4A3* or *COL4A4*	Male and Female	20%

Abbreviations: ADAS=autosomal dominant Alport syndrome; ARAS=autosomal recessive Alport syndrome; ESKD=end-stage kidney disease; XLAS=X-linked Alport syndrome

Numbers analysed

Study 1603/Phase 3

The analysis populations were as follows:

- Intent-to-treat population (ITT population):

  The ITT population is defined as all enrolled patients (N=157: 80 placebo, 77 bardoxolone methyl)

  Primary analyses of efficacy endpoints used the ITT population:

  - Primary efficacy endpoint at Week 48 (N=136: 71 placebo, 66 bardoxolone methyl)
  - Primary efficacy endpoint at Week 100 (N=138: 73 placebo, 65 bardoxolone methyl)

- Modified Intent-to-treat (mITT) population: "As-Treated" analysis of the ITT population that only includes eGFR values collected while receiving treatment (N=57 bardoxolone)

- Per-Protocol (PP) population: Year 1 PP (N=119: 66 placebo, 53 bardoxolone methyl) and Year 2 PP (N=109: 62 placebo, 47 bardoxolone methyl) were defined as patients who

  - Received study drug through Week 48 and Week 100 respectively
  - Had no protocol deviation that could potentially affect the efficacy conclusions.

  Review of protocol deviations for determining the PP population was performed by a blinded team prior to Year 1 and Year 2 database lock.

- Safety population (N=157: 80 placebo, 77 bardoxolone methyl)

It is noted that mITT only seems to be defined for the bardoxolone group.

Study 1603/Phase 2

The analysis populations were as follows:

- ITT population (N=30)
- Safety population (N=30)
- 1-year Per Protocol population (N=25)
- 2-year Per Protocol population (N=24)
- Pharmacokinetics population (N=29)

Outcomes and estimation

Change from Baseline in eGFR at Week 12

Change from Baseline in eGFR at Week 12 was the primary endpoint in the proof-of concept 1603/Phase 2 study (Table 17) but was not evaluated in the 1603/Phase 3 study. The primary endpoint of the 1603/Phase 2 study was met.

Table 17: Change from Baseline in eGFR (mL/min/1.73 m2) at Week 12 (ITT Population) (Truncated by Assessor) (Phase 2)

Statistic	Bardoxolone Methyl (N = 30)
Baseline	
N	30
Mean (SD)	54.17 (24.075)
Min, max	27.6, 94.0
Change from baseline at Week 12	
n	30
LS mean (SE)	13.37 (1.4111)
95% CI	(10.48, 16.27)
p-value	<0.0001

Abbreviations: CI=confidence interval; eGFR=estimated glomerular filtration rate; ITT=Intent-to-Treat; LS=least squares; max=maximum; min=minimum; MMRM=mixed model repeated measures; SD=standard deviation; SE=standard error
Note: All available data from all patients are used in the MMRM model.

Change from Baseline in eGFR at Week 48 and Week 100

Change from Baseline in eGFR at Week 48 and Week 100 was the primary endpoint in Study 1603 1603/Phase 3 (Table 18) and a secondary endpoint in Study 1603/Phase2 (Table 19).

Table 18: Change from Baseline in eGFR (mL/min/1.73 m^2) at Week 48 and Week 100 (ITT Population) (Phase 3)

	Placebo (N = 80)	Bardoxolone Methyl (N = 77)
Change from Baseline at Week 48[a]		
N	71	66
LS mean (SE)	-4.77 (1.248)	4.71 (1.307)
97.5% CI	-7.60, -1.95	1.75, 7.68
p-value (versus baseline)	0.0002	0.0004
LS Mean Difference [b](SE)	–	9.49 (1.813)
97.5% CI	–	5.38, 13.60
p-value (versus placebo)	–	<0.0001
Change from Baseline at Week 100[c]		
N	73	65
LS mean (SE)	-8.45 (1.478)	-0.81 (1.556)
95% CI	-11.38, -5.53	-3.89, 2.27
p-value (versus baseline)	<0.0001	0.6043
LS Mean Difference [b](SE)	–	7.65 (2.144)
95% CI	–	3.41, 11.89
p-value	–	0.0005

Abbreviations: CI=confidence interval; eGFR=estimated glomerular filtration rate; ITT=intent-to-treat; LS=least squares; MMRM=mixed models

repeated measures; SE=standard error; UACR=urinary albumin-to-creatinine ratio

a The change from baseline eGFR for patients treated with bardoxolone methyl is compared with placebo at each week using MMRM analysis, with baseline eGFR and fraction of 1 year exposure to treatment as covariates and the following fixed factors: treatment group, randomized UACR strata, time (Week 1 to Week 48), the interaction between treatment and time, and the interaction between baseline eGFR and time. The eGFR values are irrespective of whether or not the patient is receiving treatment. Within-patient errors are modeled using an unstructured covariance matrix. All available data from all patients are used in the MMRM model.
b Difference is bardoxolone methyl – placebo
c The change from baseline eGFR for patients treated with bardoxolone methyl is compared with placebo at each week using MMRM analysis, with baseline eGFR and fraction of two-year exposure to treatment as covariates and the following fixed factors: treatment group, randomized UACR strata, time (Week 1 to 100 excluding Week 52), geographical location, the interaction between treatment and time, and the interaction between baseline eGFR and time. The point estimate for each treatment group at Week 100 was based on a model that used two UACR categories (≤300 mg/g; >300 mg/g) to account for the small sample size in the two higher categories. Within-patient errors are modeled using an unstructured covariance matrix. The eGFR values are irrespective of whether or not patient is receiving treatment.

It is noted that although the primary analysis is based on the ITT population, there is a 'N' in the table indicating a much smaller number of subjects. It should be clarified if subjects are actually excluded from analysis or if the 'N' indicates subjects with actual value at the time point of analysis. If subjects are indeed excluded, a new analysis including all subjects should be provided with necessary imputation.

Table 19: Change from Baseline in eGFR (mL/min/1.73 m2) at Week 48 and Week 100 (ITT and Per Protocol Populations) (Phase 2)

Statistic	Bardoxolone Methyl		
	ITT Population	1-Year PP Population	2-Year PP Population
Baseline			
n	30	25	24
Mean (SD)	54.17 (24.075)	56.01 (24.376)	55.04 (24.406)
Min, max	27.6, 94.0	27.6, 94.0	27.6, 94.0
Change from baseline at Week 48			
n	28	25	24
LS mean (SE)	7.40 (1.9451)	10.59 (1.6672)	10.20 (1.7915)
95% CI	(3.40, 11.39)	(7.12, 14.06)	(6.67, 13.72)
p-value	0.0008	<0.0001	<0.0001
Change from baseline at Week 100			
n	23	NA	23
LS mean (SE)	4.28 (1.7484)	NA	5.54 (1.8110)
95% CI	(0.84, 7.72)	NA	(1.97, 9.10)
p-value	0.0150	NA	0.0025

Abbreviations: CI=confidence interval; eGFR=estimated glomerular filtration rate; ITT=intent-to-treat; LS=least squares; max=maximum; min=minimum; MMRM=mixed model repeated measures; NA=not applicable (2-year endpoints were not analyzed using the 1-Year PP population); PP=Per Protocol; SD=standard deviation; SE=standard error
Note: All available data from all patients are used in the MMRM model.

In both cohorts, there was a statistically significant increase in eGFR from baseline at Weeks 48 and 100. In the 1603/Phase 3 study, there was a statistically significant difference in LS mean eGFR between the treatment arms at Weeks 48 and 100. The primary endpoint of the 1603/Phase 3 study was thus met and supported by the results from the 1603/Phase 2 study.

Efficacy data for the primary endpoint was analysed by prespecified subgroups in the Phase 3 study.

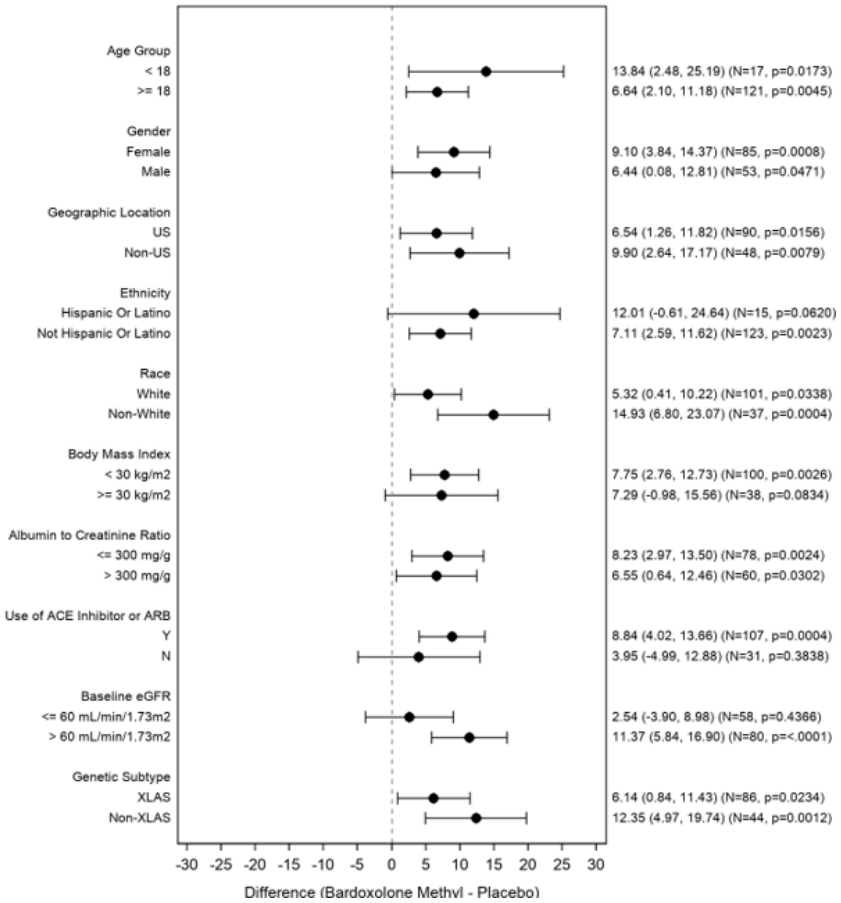
Paediatric Subgroup

The paediatric population in Study 1603/Phase 3 had a mean baseline eGFR values of approximately 70 mL/min/1.73 m^2. The paediatric subpopulation had the largest annual rates of eGFR decline prior

to study entry (-11 mL/min/1.73 m^2 per year). Treatment with bardoxolone methyl resulted in a decrease from baseline in eGFR of 1.4 mL/min/1.73 m^2 at Week 100, while treatment with placebo resulted in a decrease in eGFR of -15 mL/min/1.73 m^2. At Week 104, following a 4-week off-treatment period, mean changes from baseline in eGFR -2.9 mL/min/1.73 m^2 for bardoxolone methyl-treated paediatric patients and -18 mL/min/1.73 m^2 for placebo-treated paediatric patients

Other Subgroups

A forest plot of eGFR (mL/min/1.73 m^2) change from baseline to Week 100 (primary analysis) for prespecified subgroups is presented in Figure 8.



Note: Data shown are the LS mean differences (bardoxolone methyl - placebo), with 95% CI and p-value.
Abbreviations: ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker; eGFR=estimated glomerular filtration rate; ITT=intent-to-treat; N=no; US=United States; XLAS=X-linked Alport syndrome; Y=yes.

Figure 8: eGFR (mL/min/1.73 m^2) Change from Baseline to Week 100 by Subgroup (ITT Population) ***(Study 1603 Phase 3)***

In all prespecified subgroups, the point estimate favours bardoxolone, although not always significantly.

Of note, the subgroup of subjects with baseline eGFR ≤60 mL/min/1.73 m^2 had the poorest effect of all subgroups analysed. This can be of relevance in the discussion in extrapolation of efficacy data to subjects with CKD 4 and 5, excluded from the study population (please refer to subheading *Study participants* above)

Off-treatment Change from Baseline in eGFR at Week 52 and Week 104

Off-treatment Change from Baseline in eGFR at Week 52 and Week 104 was a key secondary endpoint the 1603/Phase 3 study (Table 20) and an exploratory endpoint in the 1603/Phase 2 study (Table 21).

The applicant has provided an extensive discussion on the off-treatment efficacy endpoint (please refer to *Justification of Off-Treatment Efficacy Endpoint* under section methods subheading *Outcomes/endpoints* above). There are indications that the 30 days off-treatment may not be sufficient for a complete washout of pharmacodynamic effects. However, as available data does not indicate a disease modifying effect, the issue whether all PD effects are gone or not after 30 days is considered somewhat less important. The main point is that the washout period and follow-up is too short to exclude long-term detrimental effects (or rebound effects) on renal function.

Table 20: Off-treatment Change from Baseline in eGFR (mL/min/1.73 m^2) at Week 52 and Week 104 (ITT Population) (Phase 3)

	Placebo (N = 80)	**Bardoxolone Methyl (N = 77)**
Change from Baseline at Week 52[a]		
N	68	66
LS Mean (SE)	-6.08 (1.243)	-0.99 (1.253)
97.5% CI	-8.87, -3.29	-3.80, 1.81
p-value (versus baseline)	<0.0001	0.4273
LS Mean difference[b] (SE)	–	5.09 (1.656)
97.5% CI	–	1.37, 8.80
p-value	–	0.0021
Change from Baseline at Week 104[c]		
N	69	56
LS Mean (SE)	-8.84 (1.353)	-4.52 (1.395)
95% CI	-11.49, -6.19	-7.26, -1.79
p-value (versus baseline)	<0.0001	<0.0012
LS Mean difference[b] (SE)	–	4.26 (1.876)
95% CI	–	0.58, 7.94
p-value	–	0.0232

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; eGFR=estimated glomerular filtration rate; ITT=intent-to-treat; LS=least squares; SE=standard error; UACR=urinary albumin-to-creatinine ratio

[a] The change from baseline eGFR for patients treated with bardoxolone methyl is compared with placebo at Week 52 using ANCOVA, with baseline eGFR and fraction of 1-year exposure to treatment as covariates and the following fixed factors: treatment group and randomized UACR strata. Missing values are imputed using multiple imputations based on the treatment group to which the patient is assigned, baseline eGFR, fraction of 1-year exposure to treatment, and randomized UACR strata.

[b] Difference is bardoxolone methyl – placebo

[c] The change from baseline eGFR for patients treated with bardoxolone methyl is compared with placebo at Week 104 using ANCOVA, with baseline eGFR and fraction of two-year exposure to treatment as covariates and the following fixed factors: treatment group, randomized UACR strata, and geographical location. The point estimate for each treatment group at Week 104 was based on a model that used two UACR categories (≤300; >300) to account for the small sample size in the two higher categories. Missing values are imputed using multiple imputations based on the treatment group to which the patient is assigned, baseline eGFR, and randomized UACR.

Table 21: Change from Baseline in eGFR Values (mL/min/1.73 m2) at Week 52 and Week 104 (Per Protocol Populations; Phase 2*)*

Statistic	Bardoxolone Methyl
Baseline (1-Year PP Population)	
n	25
Mean (SD)	56.01 (24.376)
Min, max	27.6, 94.0
Change from baseline at Week 52 (1-Year PP Population)	
n	24
LS mean (SE)	3.96 (1.8812)
95% CI	(0.05, 7.87)
p-value	0.0476
Baseline (2-Year PP Population)	
n	24
Mean (SD)	55.04 (24.406)
Min, max	27.6, 94.0
Change from baseline at Week 104 (2-Year PP Population)	
n	23
LS mean (SE)	-1.75 (1.8670)
95% CI	(-5.43, 1.92)
p-value	0.3489

The key secondary endpoint in Study 1603/Phase 3 was met. The results from the 1603/Phase 2 cohort are in support, however, not statistically significant at Week 104.

Exploratory efficacy endpoints to evaluate off-treatment impact on eGFR in Study 1603/Phase 2 were performed on the per protocol (PP) population. These analyses are less favourable for bardoxolone compared to on-treatment analyses. When comparing change from baseline (CFB) in the PP population at Week 48 and Week 52, a difference of -6.63 mL/min/1.73 m2 is observed. Similarly, when comparing CFB in the PP population at Week 100 and Week 104, a difference of -11.95 mL/min/1.73 m2 is observed. This would translate into a decline in eGFR after treatment with bardoxolone is stopped, with a more pronounced decline if the treatment duration was longer. The applicant should discuss these findings.

In a post-hoc analysis, longitudinal estimates using the off-treatment values from Year 1 and Year 2 showed annualized off-treatment eGFR slopes of -4.46 mL/min/1.73 m^2 per year for placebo patients compared to -2.32 mL/min/1.73 m^2 per year for bardoxolone methyl patients.

At the fourteenth Data Monitoring Committee (DMC) quarterly data review teleconference on September 1, 2020, DMC requested further analyses to better understand the trajectory of estimated glomerular filtration rate (eGFR) over time for patients based on treatment status. The DMC requested to review observed eGFR data only, and that off-treatment values in patients who discontinued is not to be carried forward.

The requested analyses are provided within DMC meeting minutes and generally show a steep decline in eGFR in group A (bardoxolone) in the off-treatment periods; a smaller magnitude of change from baseline in eGFR in the second year of treatment compared to the first year of treatment in patients receiving bardoxolone and overlapping CIs of eGFR between groups A and B at the end of the study

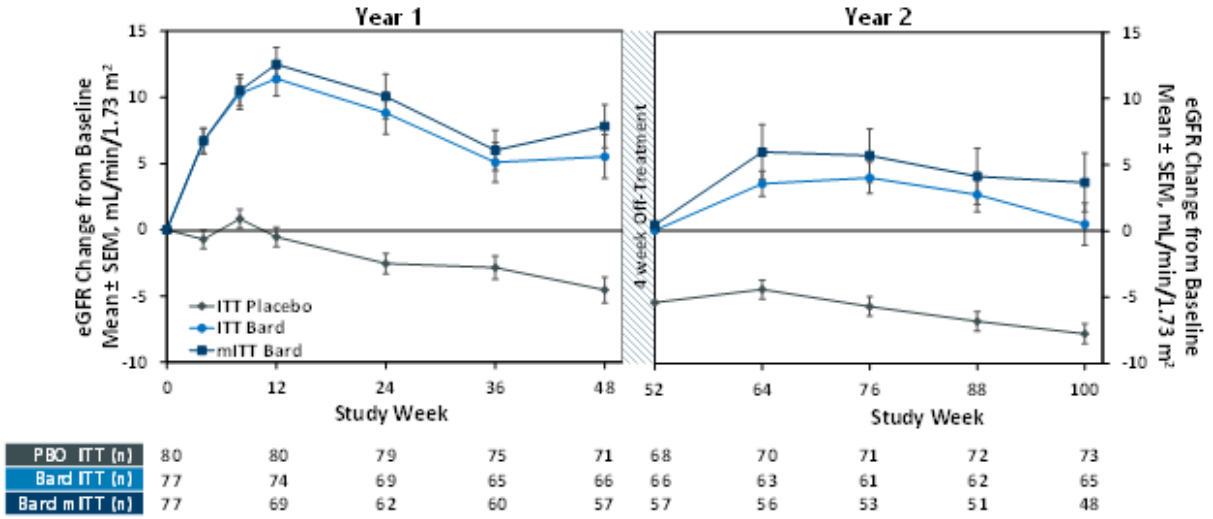
(after the second 4-week off treatment period), indicating no statistically significant difference between treatments. The exploratory nature of these analyses is acknowledged.

The applicant should present sensitivity analyses in line with the analyses requested at the fourteenth DMC quarterly data review teleconference on September 1, 2020 (i.e. observed eGFR values at each study visit and change from baseline (CFB) through the last study visit; observed eGFR using on-treatment data [any data collected after treatment discontinuation is excluded] and their CFB; eGFR using all observed values for patients who discontinued treatment and their CFB).

Continuous eGFR (eGFR Over Time)

Continuous eGFR (eGFR Over Time) was an exploratory endpoint in the 1603/Phase 3 study.

Descriptive summaries of mean on-treatment change from baseline in eGFR over time in the ITT population are shown in Figure 9. Corresponding data from the 1603/Phase 2 study is presented in Figure 10.



Abbreviations: Bard=bardoxolone methyl; eGFR=estimated glomerular filtration rate; ITT=intent-to-treat; mITT=modified intent-to-treat; PBO=placebo; SEM=standard error of the measure

Figure 9: Descriptive Summary of Change from Baseline in eGFR for Bardoxolone Methyl Versus Placebo (ITT and mITT Population) ***(Study 1603 Phase 3)***

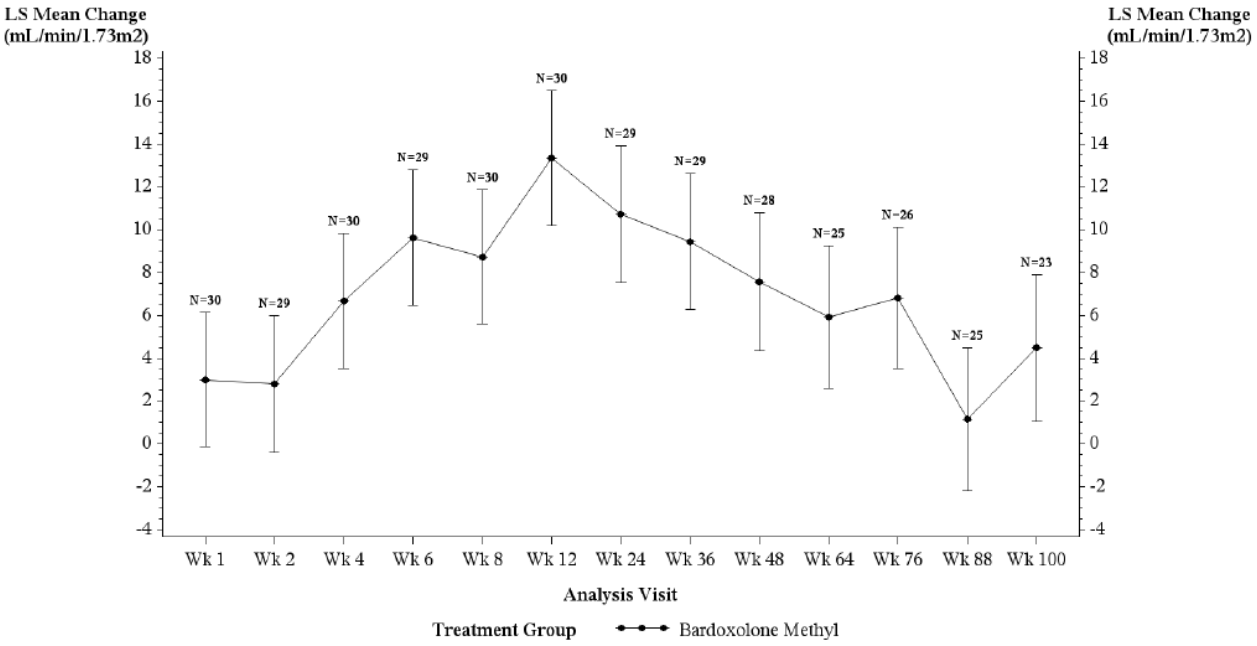


Figure 10: LS Mean eGFR Change from Baseline by Visit (ITT Population) ***(Study 1603 Phase 2)***

Please note the disproportionate timeline in Figure 10 with the first six observations representing Week 1-12 and the following seven observations Week 24-100 with 12 weeks between each observation.

During the first twelve weeks of bardoxolone treatment, eGFR is improved with over 10 mL/min/1.73 m2 compared to baseline in both the Phase 2 and Phase 3 cohorts. After the initial improvement, eGFR in the bardoxolone arm falls from Week 12 to Week 48 at a rate visually not largely differing from that in the placebo arm.
Treatment that slows disease progression should change the trajectory of the decline in kidney function, whereas reversible pharmacodynamic treatment effects would change eGFR upon initiation of treatment but would not change the trajectory of the disease course. In the latter situation, the effect on eGFR would wean off at treatment interruption after the pharmacodynamic effect has fully reversed. As discussed elsewhere, the applicant claims that the initial improvement on bardoxolone treatment is not caused by an increase in intraglomerular pressure but by an increasing glomerular surface area, by reversing endothelial dysfunction and by mesangial cell contraction. There is also assumed to be an effect on inflammation and fibrosis. However, the trajectory of eGFR over time does not support any long-term disease modifying effect. A discussion regarding clinical relevance of the transient rise in eGFR is requested.

There is some concern regarding long term date with regard to renal function. Few patients have been exposed to longer treatment periods than two years (see interim data from long-term Study 1803 below), and although the slopes appear parallel during the placebo-controlled period, there are scarce data available to exclude more rapid deterioration of GFR over time. Of note, in non-clinical study RTA-P-19006 in mice, 28 animals were euthanized or found dead prior to the scheduled necropsy. Of these 28 animals, 27 had gross necropsy findings in the kidney. The applicant claims that the toxicity seen in rodents (mouse, rat and hamster) is caused by a rodent-specific metabolism. A question on kidney findings in the non-clinical setting has been raised in the non-clinical section. Furthermore, the metabolism in humans and potential occurrence of (toxic) metabolites is not fully elucidate (see Pharmacokinetic MO). In this context, it is also noted that bardoxolone treatment was related to an increase in the urine albumin creatinine ratio (UACR). It is agreed with the applicant that an increase in glomerular filtration could lead to an increase in albuminuria. Notwithstanding, in such case, the excretion of creatinine is expected to raise in parallel. In the case of bardoxolone, UACR is raised,

indicating a relative increase in albuminuria to creatinine excretion. Considering that albumin excretion is a well described surrogate marker for glomerular damage. This needs further discussion.

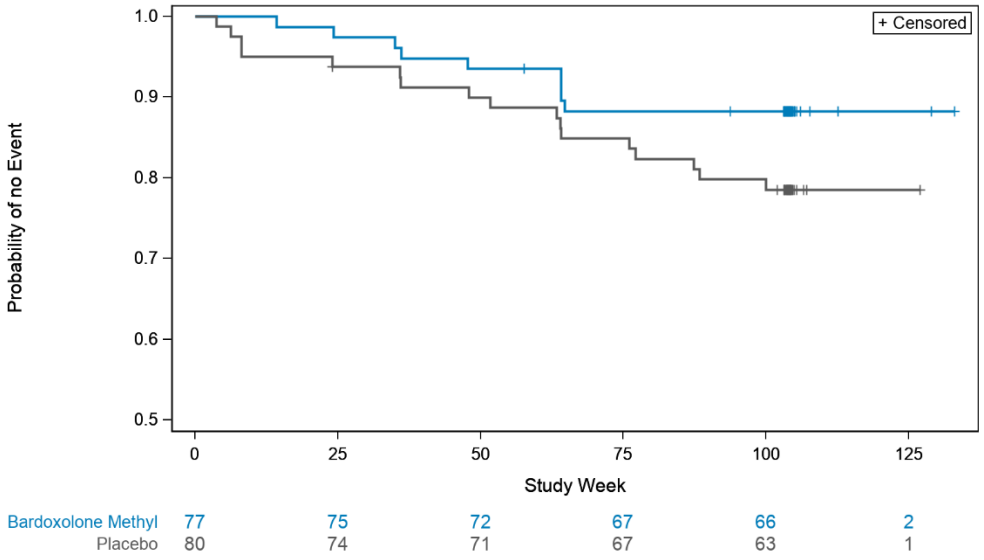
The applicant should present further long-term data as available and discuss the possibility of detrimental long-term effect of treatment. In this context possible rebound effects upon treatment cessation should be discussed. Furthermore, the applicant should discuss whether a direct effect of bardoxolone on the podocytes resulting in an alteration in the filtration barrier can be excluded. The applicant is also asked to discuss whether an increase in UACR has been reported in other products intended for renoprotection.

Exploratory Efficacy Analysis: Kidney Failure Composite Outcome

An exploratory composite endpoint reflecting the risk for kidney failure was introduced in the 1603/Phase 3 study. Use of both ≥30% decline in eGFR and eGFR <15 mL/min/1.73 m^2 have been validated as surrogates for progression to End stage kidney disease (ESKD) [*Assessor's comment*: ESRD and ESKD are used synonymously] to be used in clinical trials. Study 1603/Phase 3 used kidney failure endpoint as composite of one of the following events: ≥30% decline from baseline in eGFR, eGFR <15 mL/min/1.73 m^2, or ESKD (initiation of maintenance dialysis or kidney transplant).

Table 22: Number and Percent of Patients with a Kidney Failure Event (ITT Population) (Phase 3)

	Placebo (N = 80)	Bardoxolone Methyl (N = 77)
Kidney Failure Composite Event: Confirmed Cases	17 (21.3%)	9 (11.7%)
ESKD (initiation of maintenance dialysis or kidney transplant)	3 (3.8%)	3 (3.9%)
Confirmed eGFR < 15 mL/min/1.73 m^2 [d]	3 (3.8%)	2 (2.6%)
Confirmed 30% decline from baseline in eGFR[e]	17 (21.3%)	9 (11.7%)



Note: Kidney failure composite event is defined as the occurrence of any one or more of the following events: 30% decline from baseline in eGFR, GFR <15 mL/min/1.73 m^2, or ESKD (initiation of maintenance dialysis or kidney transplant). A 30% decline or eGFR <15 mL/min/1.73 m^2 is considered confirmed when the threshold is achieved at 2 or more visits. Patients who achieved the threshold at their last visit, but did not have a second confirmatory visit, are considered as confirmed cases in this plot.

Figure 11: Time-to-Event Analysis for Kidney Failure Composite Outcomes in Study 1603 Phase 3

Patients in the bardoxolone methyl group had approximately 50% fewer confirmed kidney failure events compared with the placebo group (9 patients versus 17 patients in placebo, with a hazard ratio of 0.49 estimated from Cox Regression stratified by randomized UACR and a ChiSq p-value of 0.086) (Figure 11). Of note, there was no difference in the reporting of ESRD between the treatment arms.

The composite outcome includes individual components of unequal clinical significance (ESRD, eGFR <15 mL/min/1,73 m2 and 30% decline from baseline in eGFR). The difference between the two treatment arms is driven by the difference in the least clinically relevant outcome (30% decline in eGFR), while there is no difference in other, more clinically relevant components of this outcome. Progression to ESRD was observed in 3 patients in placebo and 3 patients in bardoxolone groups, while eGFR <15 was observed in 3 patients in placebo and 2 in bardoxolone arms. The applicant should discuss the relevance of 30% decline from baseline in eGFR in describing kidney failure event, especially considering very broad baseline eGFRs in study population.

Mean time to kidney failure composite event for the placebo group is 89.2 (SE 2.9) weeks, and for the bardoxolone methyl group is 62.5 (SE 1.0) weeks. Analysis of time to First Kidney Failure Event shows lack of a statistically significant difference between patients treated with placebo and bardoxolne (HR 0.493 (95% CI 0.2, 1.1; p=0.086). It seems that kidney failure outcomes occur approximately 27 weeks earlier in patients on treatment and it might imply that bardoxolone methyl causes faster deterioration of renal function, especially in patients with already poor parameters of kidney function (low baseline eGFR and high baseline UACR). The applicant should provide a discussion on this issue.

In the 1603/Phase 2 study, three patients progressed to ESRD, six had an eGFR decline of 30% at two or more visits, and three had eGFR <15 mL/min/1.73 m2 at 2 or more visits. The mean (SE) time to disease progression was 574.0 (21.15) days.

The demography of nine subjects developing ESRD in Study 1603 is summarised in Table 23. Of note, all subjects had baseline eGFR in the lower spectrum (27-41 mL/min/1.73 m2) and high baseline UACR (882-2207 mg/g), both factors representing a high risk for disease progression.

Table 23: End Stage Renal Disease SAEs (Phase 2 and 3)

Study Treatment Subject	Age (yrs)	Treatment			Baseline eGFR mL/ min.1.73m2	Baseline UACR (mg/g)	Action taken	AE (Study Day)	
		Group	Start	Stop[b]				Start	Stop
402-C-1603 Phase 3									
[redacted]	16	Placebo	19 Jun 2018	03 Apr 2019	31.9	1367	Drug withdrawn	04 Apr 2019 (290)	16 Apr 2019 (302)
[redacted]	17	Placebo	01 Aug 2018	30 Jun 2019	37.7	1190	None	09 Mar 2020 (587) Not TEAE	27 Apr 2020 (636)
[redacted]	42	Placebo	27 Oct 2017	25 Sep 2018	26.9	1835	Dose not changed	18 Jan 2018 (84)	07 Dec 2018 (407)
[redacted]	45	Bardoxolone methyl 30 mg	23 Mar 2018	03 Nov 2019	37.3	1136	Drug withdrawn	04 Nov 2019 (592)	04 Nov 2019 (592)
[redacted]	18	Bardoxolone methyl 30 mg	02 May 2018	11 Feb 2019	31.2	1471	None	15 Apr 2019 (349) Not TEAE	26 Dec 2019 (604)
[redacted]	32	Bardoxolone methyl 30 mg	06 Jun 2018	18 Feb 2019	32.1	2207	Drug withdrawn	21 Feb 2019 (261)	17 Dec 2019 (560)
402-C-1603 Phase 2									
[redacted]	22	Bardoxolone methyl 30 mg	13 Jul 2017	16 Jul 2018	31.2	1326	Drug withdrawn	17 Jul 2018 (370)	19 Jul 2018 (372)
[redacted]	35	Bardoxolone methyl 30 mg	18 Jul 2017	12 Jun 2019	40.7	1539	Drug withdrawn	15 Jun 2019 (698)	02 Aug 2019 (746)
[redacted]	44	Bardoxolone methyl 30 mg	22 Mar 2017	15 Feb 2019	26.9	882	Drug withdrawn	19 Feb 2019 (700)	23 Feb 2019 (704)

Abbreviation: ESRD = end stage renal disease; eGFR = estimated glomerular filtration rate, TEAE = treatment-emergent adverse event, UACR = Urinary albumin-to-creatinine ratio

[a] Patient [redacted] (placebo) indicated that the onset of the end stage renal disease began while on study drug. No action with study drug was reported.

[b] Treatment end date is based on ISS Listing 16.1.1, It is noted that the end of treatment dates in ISS Listing 16.8.2 are different for Subjects [redacted] and [redacted] as they were imputed as these patients' kits were not returned

Source: ISS Listing 16.1.1; ISS Listing 16.9.1; ISS Listing 16.11.1; ISS Listing 16.12.1

The significantly higher proportion of patients from 1603/Phase 2 compared to Phase 3 progressing to ESRD requires clarification. The applicant should: a) confirm that all three patients progressing to ESRD in Phase 2 were included in analyses at Week 12 and analyses at all subsequent timepoints; b) confirm that all patients progressing to ESRD in Phase 3 trial (3 in bardoxolone and 3 in placebo) were included in analyses at all timepoints; c) should confirm that all cases of ESRD have been identified and reported and should present new cases of ESRD (other than the 9 mentioned above) if applicable and d) discuss the larger proportion of patients from Phase 2 study progressing to ESRD compared to patients from Phase 3 progressing to ESRD. The progression to ESRD observed in Phase 2 cohort during treatment with bardoxolon is concerning and requires further elucidation.

3.3.4.1. Summary of main efficacy results

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 24: Summary of efficacy for trial "CARDINAL": A Phase 2/3 trial for the efficacy and safety of bardoxolone methyl in patients with Alport syndrome (Phase 3 cohort)

Title: "CARDINAL" A Phase 2/3 trial for the efficacy and safety of bardoxolone methyl in patients with Alport syndrome (Phase 3 cohort only)			
Study identifier	Study 1603		
Design	Study 1603 Phase 3 was a multi-centre, double-blind, randomised (1:1), placebo-controlled study conducted in the US, Australia, France, Germany, Japan, Spain, and United Kingdom		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		104 weeks including 6 weeks of dose escalation. "Off treatment windows" Week 48-52 and Week 100-104 Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Bardoxolone		Starting dose 5 mg QD (5 mg Q2D in the paediatric population), increased stepwise during six weeks to 20 mg QD (screening UACR ≤300 mg/g) or 30 mg (screening UACR >300 mg/g) N=77
	Placebo		Placebo administered in increments as above. N=80
Endpoints and definitions	Primary endpoint	Week 48; Week 100	Difference in change from baseline in eGFR (mL/min/1.73 m2) at Week 48 and at Week 100
	Key Secondary endpoint	Week 52; Week 104	Difference in change from baseline in eGFR (mL/min/1.73 m2) at Week 52 and at Week 104 (after four weeks off treatment)
Database lock	Study completed. Last patient last visit: 30 October 2020, Date of final study report: 12 February 2021		
<u>Results and Analysis</u>			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Population: Intent to treat Timepoint: Week 48 and Week 100 (primary endpoint) Week 52 and Week 104 (key secondary endpoint)		
Descriptive statistics	Treatment group	Bardoxolone	Placebo

Title: "CARDINAL" A Phase 2/3 trial for the efficacy and safety of bardoxolone methyl in patients with Alport syndrome (Phase 3 cohort only)			
Study identifier	Study 1603		
and estimate variability	Number of subjects	Week 48: n=66 Week 100: n=65 Week 52: n=66 Week 104 n=56	Week 48: n=71 Week 100: n=73 Week 52: n=68 Week 104: n=69
	Week 48 (LS mean [SE])	4.71 (1.307)	-4.77 (1.248)
	97.5% CI	1.75, 7.68	-7.60, -1.95
	Week 100 (LS mean [SE])	-0.81 (1.556)	-8.45 (1.478)
	95% CI	-3.89, 2.27	-11.38, -5.53
	Week 52 (LS mean [SE])	-0.99 (1.253)	-6.08 (1.243)
	97.5% CI	-3.80, 1.81	-8.87, -3.29
	Week 104 (LS mean [SE])	-4.52 (1.395)	-8.84 (1.353)
	95% CI	-7.26, -1.79	-11.49, -6.19
Effect estimate per comparison	Primary endpoint Week 48	Comparison groups	Bardoxolone vs placebo
		LS Mean Difference (SE)	9.49 (1.813)
		97.5% CI	5.38, 13.60
		P-value vs placebo	<0.0001
	Primary endpoint Week 100	Comparison groups	Bardoxolone vs placebo
		LS Mean Difference (SE)	7.65 (2.144)
		95% CI	3.41, 11.89
		P-value vs placebo	0.0005
	Secondary endpoint Week 52	Comparison groups	Bardoxolone vs placebo
		LS Mean Difference (SE)	5.09 (1.656)
		97.5% CI	1.37, 8.80
		P-value vs placebo	0.0021
	Secondary endpoint	Comparison groups	Bardoxolone vs placebo

Title: "CARDINAL" A Phase 2/3 trial for the efficacy and safety of bardoxolone methyl in patients with Alport syndrome (Phase 3 cohort only)			
Study identifier	Study 1603		
	Week 104	LS Mean Difference (SE)	4.26 (1.876)
		95% CI	0.58, 7.94
		P-value vs placebo	0.0232
Notes			

Abbreviations used: CI=confidence interval, eGFR estimated glomerular filtration rate, ITT intention to treat, SE=standard error, QD every day, Q2D every second day, SE=standard error, UACR urine albumin/creatinine ratio

3.3.4.2. Clinical studies in special populations

There were three subjects aged ≥65 years of age (65, 68 and 70 years old) in the controlled Phase 3 study and none in the uncontrolled Phase 2 study.

3.3.4.3. In vitro biomarker test for patient selection for efficacy

Not applicable

3.3.4.4. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

3.3.4.5. Supportive studies

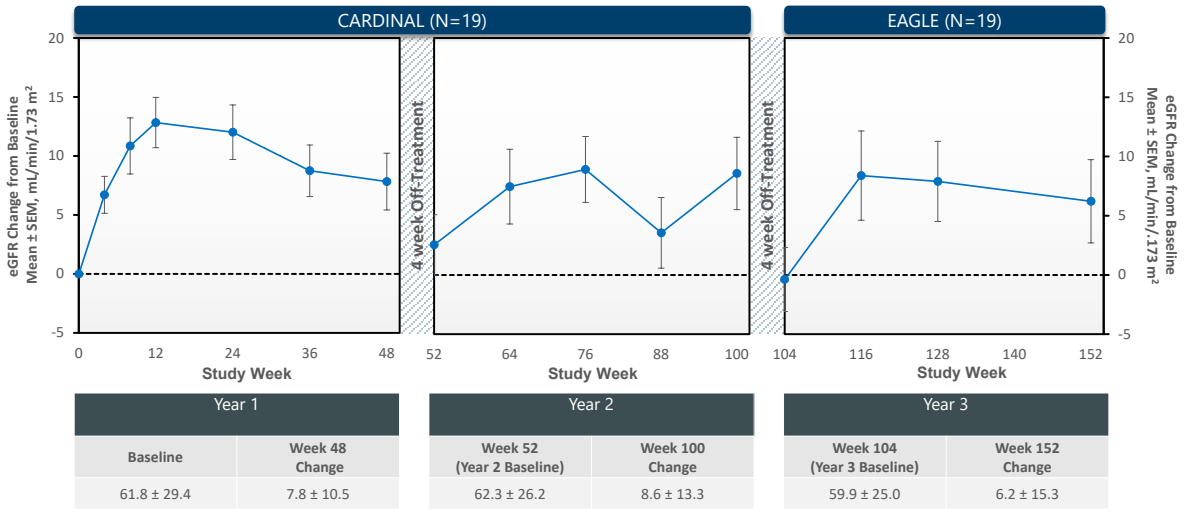
Key Efficacy Findings from Study 1803

Study 1803 is an ongoing long-term study eligible for subjects from Phase 2 or Phase 3 (placebo and bardoxolone) of Study 1603. The primary objective of Study 1803 is long-term safety. The study is planned to continue until bardoxolone is commercially available.

Patients eligible for inclusion had no serious AEs during the initial studies and are believed to have a positive benefit-risk for participating in this trial. Patients with a pronounced eGFR decline or reaching ESRD or nephrotic syndrome were not to be included. The inclusion/exclusion criteria appear to limit the eligible population to the group of previously treated patients who are likely to benefit most from the treatment. As such, any potential future efficacy suggestions derived from this study are severely hampered by the presence of selection bias.

As of the 18 January 2021 interim database lock date, 96 patients had been enrolled in Study 1803. Of the 96 patients, 94 were continuing to receive treatment and two patients had discontinued from treatment and from the study. Of the patients who received bardoxolone methyl for 2 years in Study 1603 Phase 2 and Phase 3, 50 continued to receive bardoxolone methyl treatment in Study 1803 (17 from Study 1603/Phase 2 and 33 from Study 1603/Phase 3). Of note, 65 subjects contributed to the bardoxolone ITT population at Week 100 in the Study 1603/Phase 3. The corresponding number for the Study/1603 Phase 2 was 23 subjects. If available, the applicant is asked to present a summary to why over 25% of the ITT population in the Phase 2 and 50% of the bardoxolone ITT population of the 1603/Phase 3 study chose not to enter the long-term study.

Twenty-seven patients have completed through Week 48 in Study 1803 and 19 of these patients had approximately 3 years of exposure to bardoxolone methyl (48 weeks of exposure in Study 1803 and 2 years of the exposure in a prior qualifying study) (Figure 12).



Note: Data observed are mean ± SD changes from baseline in eGFR. Changes in eGFR in Year 2 and Year 3 eGFR are calculated relative to Year 1 baseline. Abbreviations: eGFR=estimated glomerular filtration rate; SD=standard deviation.

Figure 12: Study 1803: Change from Baseline in eGFR after 1, 2, and 3 Years of Treatment with Bardoxolone Methyl (19 Patients with 3 Year Data)

For the 19 subjects so far completing in total three years of bardoxolone treatment, i.e., 104 weeks in one of the feeder studies plus 52 weeks in Study 1803, a similar pattern was seen after resuming bardoxolone treatment at Week 104, with an initial increase in eGFR during the first 12 weeks and a subsequent slower fall in eGFR. It is reassuring to note that subjects entering Study 1803 after previous bardoxolone treatment in Study 1603 are still over baseline in the feeder study at Week 152 for treatment start. The applicant is asked to provide any data on eGFR from Study 1803 available after the data lock point of this submission.

On-Treatment Changes in eGFR in Supporting Studies from other populations

In addition to the improvements in eGFR observed in patients with Alport syndrome, clinical effects of bardoxolone methyl have also been observed in patients with Autosomal dominant polycystic kidney disease (ADPKD), Immunoglobulin A nephropathy (IgAN), Focal segmental glomerulosclerosis (FSGS), and diabetic nephropathy. Table 25 shows changes in eGFR from the supporting studies. Except where noted, the data are mean changes from baseline for bardoxolone methyl patients and p-values are calculated from 2-sided paired t-tests comparing eGFR change to 0.

Table 25: Changes from Baseline in eGFR in Supporting Studies of Chronic Kidney Diseases

Study	*Phase/ Country*	*Study Population*	*Number of Patients*	*Treatment Duration*	*Change in eGFR (mL/min/1.73 m²)*
RTA402-005	2/ Japan	T2D and Stage 3 and 4 CKD	120	16 weeks	6.6 (inulin GFR)[a] (p=0.008 vs PBO)
402-C-1702	2/US	ADPKD	31	12 weeks	9.3 (p<0.0001)
		IgAN	26	12 weeks	8.0 (p<0.0001)
		T1D CKD	28	12 weeks	5.5 (p=0.025)
		FSGS	18	12 weeks	7.8 (p=0.003)
402-C-1102	1/US	T2D and Stage 3b and Stage 4 CKD	24	56 days	9.0 (p<0.05)
402-C-0903	3/Global	T2D and Stage 4 CKD	2185	Median: 7 months with 522 patients through Week 48	6.4[a] (p<0.001 vs PBO) CrCl also sig. increased
402-C-0902	2/US	T2D and CKD	131	85 days	6.5 (p<0.001)
402-C-0804	2/US	T2D and CKD	227	52 weeks	8.6 at Week 52[a] (p<0.001 vs PBO)
402-C-0801 (Stratum 2) (open label)	2b/US	Diabetic nephropathy	20	56 days	7.2 (p<0.001) CrCl also sig. increased
402-C-0801 (Stratum 1) (open label)	2a/US	Diabetic nephropathy	60	28 days	6.7 (p<0.001)

Abbreviations: ADPKD=autosomal dominant polycystic kidney disease; CKD=chronic kidney disease; CrCl=creatinine clearance; eGFR=estimated glomerular filtration rate; FSGS=focal segmental glomerulosclerosis; GFR=glomerular filtration rate; IgAN=immunoglobulin A nephropathy; PBO=placebo; sig.=significantly; T1D=type 1 diabetes; T2D=type 2 diabetes; US=United States
a Placebo-corrected change from baseline.

Two of these studies (Studies 402-C-0804 and 402-C-0903) showed that on-treatment increases from baseline in eGFR in patients with CKD who are treated with bardoxolone methyl were sustained for at least 1 year (Figure 13). In Study 402-C-0903, increases in eGFR with bardoxolone methyl were durable for up to a year of treatment.

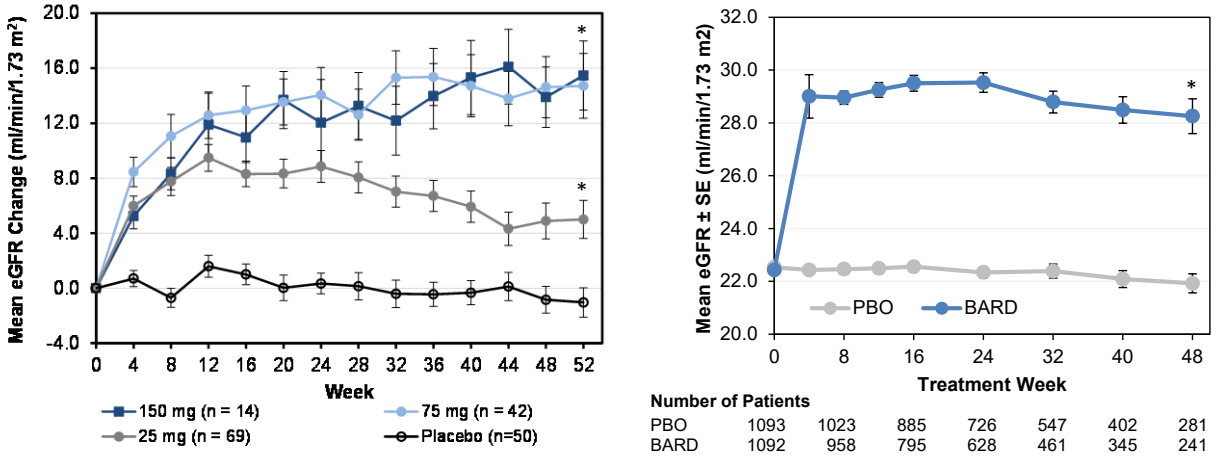


Figure 13: Studies 402-C-0804 and 402-C-0903: Mean eGFR Through One Year in Patients with Type 2 Diabetes and Chronic Kidney Disease

Notes: Left: Mean observed eGFR changes from baseline (±SEM) in patients in Study 402-C-0804 who continued dosing through Week 52 grouped by actual dose received at Week 52. * p < 0.001 versus placebo. Right: Mean observed eGFR (±SEM) over time by treatment week in placebo versus bardoxolone methyl patients in Study 402-C-0903. Figure includes only assessments of eGFR collected on or before administration of a patient's last dose of study drug. * p<0.001 versus placebo.
Abbreviations: BARD = bardoxolone methyl; eGFR=estimated glomerular filtration rate; PBO = placebo; SEM=standard error of the measure.

As demonstrated in the Alport development program, a rapid increase was seen during the first 8-12 weeks of treatment in two studies in subjects with T2DM and CKD. Study 0804 used the crystalline formulation yielding approximately three times lower AUC than the amorphous SDD formulation used in the newer studies, explaining the apparently higher dosing in this study. Of note, the two higher doses in Study 0804 resulted in a sustained increase in eGFR through the study. A similar effect was seen in Study 0903, using 20 mg of the amorphous SDD formulation. In this case, however, the decline in renal function was slow also in the placebo arm.

Off-Treatment Changes in eGFR from Supporting Studies

In addition to the off-treatment data from the Phase 3 and Phase 2 studies in patients with Alport syndrome described above, off-treatment data have also been assessed for bardoxolone methyl in patients with T2D and CKD in Studies 402-C-0804 and 402-C-0903. In these prior studies, patients participated in a 4-week withdrawal period following treatment with bardoxolone methyl for at least one year, as described below.

In Study 402-C-0804, analysis of the change in eGFR from baseline to Week 56 for patients who received study drug for 52 weeks showed that some of the on-treatment increase in eGFR is retained following withdrawal of therapy (Table 26).

Table 26: Study 402-C-0804 and Study 402-C-0903: Mean eGFR Change from Baseline at End of Treatment and Four Weeks Post-Treatment Withdrawal

Mean eGFR Change from Baseline ± SEM (mL/min/1.73 m²)				
Dose	**N[a]**	**Baseline eGFR**	**End of Treatment**	**4 Weeks Post-Withdrawal**
402-C-0804				
Placebo	49	31.8	-1.0 ± 1.1	-0.7 ± 1.1
25 mg	68	33.2	5.2 ± 1.4	-0.1 ± 1.2
75 mg	41	32.3	14.9 ± 2.4	4.0 ± 1.8[b]
150 mg	14	31.8	15.5 ± 2.5	4.3 ± 2.4
402-C-0903				
Placebo	273	22.5	-1.2 ± 0.3	-0.8 ± 0.3
Bardoxolone methyl	225	22.4	5.7 ± 0.6[c]	1.0 ± 0.5[c]

Abbreviations: eGFR=estimated glomerular filtration rate; SEM=standard error of the measure.
[a] For Study 402-C-0804, N is the number of patients with data at Week 52 and Week 56 by the dose received at Week 52; for Study 402-C-0903, N is the number of patients receiving at least 48 weeks of treatment with 4-week post-withdrawal data.
[b] p <0.05 versus placebo.
[c] p <0.001 versus placebo.
Source: Study 402-C-0804, Table 14.2-56; Study 402-C-0903, Table 32; Chin, 2018

The off-treatment data from Study 402-C-0804 and Study 402-C-0903 are consistent with the findings from study 1603.

3.3.4.6. Evaluation of Adverse Kidney Outcomes

The primary endpoint for Study 402-C-0903 was a time-to-event analysis of a composite endpoint of ESKD (chronic dialysis, kidney transplant or renal death) and cardiovascular death (i.e., the primary composite outcome). Because the study was terminated early after accrual of only approximately one-third of the planned events, too few events occurred to reliably determine the drug's true effect on delaying the risk for ESKD. Nevertheless, numerically fewer ESKD events were observed in the bardoxolone methyl group than in the placebo group (43 versus 51, respectively; Table 27).

Table 27: Study 402-C-0903: Patients Meeting the Primary Composite Outcome (ITT Population)

Composite Primary Efficacy Outcome	Placebo (n=1097)	Bardoxolone Methyl (n=1088)
ESKD events	51 (5%)	43 (4%)
Chronic dialysis	47 (4%)	40 (4%)
Kidney transplant	3 (<1%)	1 (<1%)
Renal death	1 (<1%)	2 (<1%)
Cardiovascular death	18 (2%)	26 (2%)

Abbreviations: ESKD=end-stage kidney disease; ITT=Intent-to-treat
Source: Study 402-C-0903 CSR, Table 11.4.1.1-1.

Additionally, a post-hoc analysis was performed on the study results using the two endpoints that have been established as valid surrogates for progression to kidney failure for clinical trials of CKD (i.e., ≥ 30% decline in eGFR and eGFR < 15 mL/min/1.73 m^2) (Figure 14).

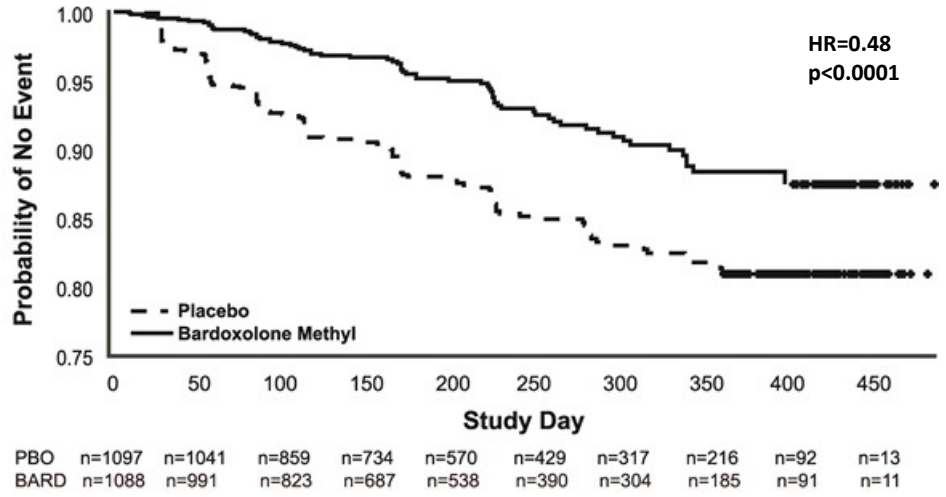


Figure 14: Study 402-C-0903: Time to First Event for the Composite Primary Efficacy Outcome

Notes: Kaplan-Meier plots of the time-to-first-event for a renal composite consisting of ≥ 30% decline from baseline in eGFR, eGFR < 15 mL/min/1.73 m^2, and adjudicated ESKD events Top: ≥30% decline from baseline in eGFR, eGFR <15 mL/min/1.73 m^2, and adjudicated ESKD events; **Bottom**: ≥30% decline from baseline in eGFR and eGFR <15 mL/min/1.73 m^2. Hazard ratios and 95% confidence intervals were computed using Cox proportional-hazards regression models. Median duration of exposure to the study drug was 7 months for patients randomized to bardoxolone methyl and 8 months for patients randomized to placebo.
Abbreviations: BARD=bardoxolone methyl; eGFR=estimated glomerular filtration rate; ESKD=end-stage kidney disease; HR=hazard ratio; PBO=placebo.

In the BEACON study, which was terminated early due to safety issues, there was no significant difference in the proportion of subjects meeting a composite endpoint of ESKD (chronic dialysis, kidney transplant or renal death). It should however be noted that only approximately one third of the planned sample size were included when the study was closed. Furthermore, a post hoc analysis

indicates a positive effect of bardoxolone on the risk of developing ≥ 30% decline in eGFR or eGFR < 15 mL/min/1.73 m2). This is of interest, but data needs to be taken with some caution, as this was a post hoc analysis.

3.3.5. Discussion on clinical efficacy

Bardoxolone methyl is an orally bioavailable activator of the transcriptor factor Nuclear factor erythroid 2-related factor 2 (Nrf2) activator. Bardoxolone methyl targets the Keap1-Nrf2 pathway, which plays a key role in the resolution phase of inflammation by regulating the expression of genes involved in redox balance. Genetic research data in humans demonstrate that the Keap1-Nrf2 pathway is suppressed in many forms of chronic kidney disease (CKD), including Alport syndrome, and is an important correlate with GFR.

Alport syndrome is a rare, rapidly progressive genetic kidney disease caused by mutations in one of three genes encoding the α3, α4, and α5 chains of Type IV collagen. The different mutations result in different inheritance pattern. The most common inheritance pattern is X linked Alport syndrome (XLAS). The severity of disease differs by the inheritance pattern and the nature of the causative mutation. As per data from National Organization for Rare Disorders/Alport Syndrome Foundation, approximately 50% of untreated males with XLAS develop kidney failure by age 25. The lifetime risk for ESRD in male subjects with XLAS is 100% compared to 25% in female subjects. The lifetime risk for ESRD in both males and females is 100% in autosomal recessive (ARAS) and 20% in autosomal dominant (ADAS).

Current treatment recommendations for the decline of kidney function in patients with Alport syndrome include treatment with inhibitors of the RAAS pathway (e.g., ACEi and/or ARBs). Imbarkyd has been administered both with and without RAAS inhibition in the Alport studies and is not intended as an alternative treatment, but a complement, to RAAS inhibition. There is a strong unmet need for additional therapies targeting the rapid deterioration of renal function in Alport syndrome with its high risk of developing ESRD at a young age.

Efficacy data for bardoxolone for the treatment of chronic kidney disease (CKD) caused by Alport syndrome in adults and adolescents aged 12 years and above were mainly obtained from three clinical studies: Study 1603/Phase 3, Study 1603/Phase 2, and Study 1803. Supportive data were presented from studies with bardoxolone in subjects with CKD due to other conditions, mainly diabetes.

Design and conduct of clinical studies

The pivotal Study 1603 Phase 3 was a double-blind, randomised, placebo-controlled study in patients aged 12 to 70 years with Alport syndrome with a duration of 104 weeks. The primary objective was the change in eGFR from baseline at Week 48 and Week 100. Study 1603/Phase 2 was an open-label and uncontrolled study using the same posology as the Phase 3 cohort, intended to provide proof of concept data at Week 12 before launching the Phase 3 study. The duration of the 1603/Phase 2 study was 104 weeks, thereby providing additional efficacy and safety data. Study 1803 is an ongoing long-term study eligible for subjects from 1603/Phase 2 or1603/Phase 3 (placebo and bardoxolone) of Study 1603. The primary objective of Study 1803 is long-term safety.

The design of Study 1603/Phase 3 has previously been discussed with EMA in a Protocol Assistance procedure (EMA/CHMP/SAWP/599796/2018) and the advice has generally been followed. Notwithstanding, there are some issues in need of further discussion concerning design and conduct of the study as summarised below. Concerns are raised regarding study conduct that have the potential of affecting the integrity of the study and validity of the data acquired. Extensive protocol changes were made well into the duration of the study.

The Sponsor decided to unblind themselves after completion of the first year of treatment. This was not foreseen in the Protocol and its amendments; instead, it was foreseen by a Data Access Plan dated 15 August 2019, introduced approximately 8 months after the last patient was randomised into the trial. Concerns were raised by the DMC regarding integrity of the data and ethics behind such actions. Concerns regarding the internal validity of the pivotal trial are further emphasised in light of public release of Year 1 data on November 11, 2019. The sponsor had not produced any of the plans or documents requested priorly by the DMC including re-consent documents for study participants, communication plan to study participants, investigators and Institutional Review Boards. The Sponsor did not agree to re-consent patients following the publication of Year 1 results. The DMC expressed feeling pressured by the sponsor to recommend stopping the trial without a prespecified stopping rule or safety concerns, which is also ethically troublesome. Final meeting minutes seem to be missing. All of these actions should be discussed on ethical grounds.

Major protocol deviations were recorded in most of the patients. Over 20% of participants had a protocol deviation regarding informed consent. Over 20% of participants had protocol deviations which included failure of informing PI of weight gain**,** and failure of having an unscheduled assessment and/or increasing BNP or transaminases. This is of concern, as fluid retention and elevated liver enzymes are adverse events of special interest for bardoxolone. The applicant should inform if a pattern in these deviations was observed (i.e.. clustering in any particular study centre or at any particular timepoint). If any of these deviations led to subsequent permanent withdrawal of the informed consent should also be stated. In addition, the applicant should present a list of all AEs recorded in patients who had a major protocol deviation related to failure of informing PI of weight gain and should explain steps taken to ensure safety of those patients.

Dosing

Development of bardoxolone methyl capsules began with a crystalline formulation. However, owing to low bioavailability, an amorphous SDD formulation was developed. Study 1603 Phase 2/3 was performed with the amorphous SDD formulation, which is also the intended commercial product.

There were no dose finding studies in subjects with Alport syndrome. Dosing in Study 1603 was based on results from a dose-ranging study in diabetic CKD subjects (Study 0902), comparing five doses (2.5 mg, 5 mg, 10 mg, 15 mg, and 30 mg, all given once daily) and on the subsequent BEACON study.

The degree of comparability between patients with different diseases (CKD in T2DM, diabetic nephropathy vs Alport syndrome) with respect to pharmacokinetic parameters influencing the optimal dose is unclear; however important differences seem plausible.

The posology used in study 1603, also proposed for the commercial product, was an increase over six weeks from 5 mg daily (5 mg every other day in subjects under the age of 18 years of age) to a target dose of 20 mg or 30 mg, depending on baseline levels of albuminuria. Despite some uncertainties, as discussed in 3.3.4.1. , the use of 20-30 mg bardoxolone can be considered accepted from an efficacy point of view. Despite the cardiac safety issues in Study 0903, the safety data from Study 0902 did not indicate a worse safety profile in the 30 mg arm, thereby supporting the use of the higher dose. However, support for using two target doses is not fully clear. The applicant justifies different target doses in subjects with baseline urinary albumin/creatinine ratio (UACR) ≤300 mg/g and >300 mg/g with results from Studies 0902 and 0903. These data were not summarised for easy assessment in the file and comparisons between the outcome at different time points in the two UACR subgroups in the CSR of Study 0902 is difficult to overview. The applicant is asked to present data supporting the differentiated dosing in a concise and assessable way**.**

The dosing schedule proposed for marketing is more gradual compared to the dosing schedule tested in Phase 2/3 trial. This also means that the dosing schedule proposed for marketing has not been

tested in any clinical trial in the intended indication. The applicant should discuss and justify the proposed dosing schedule including reasons and data underpinning the more gradual dosing scheme proposed for marketing compared to dosing in both Phase 2/3 trial.

Study population

The diagnosis of Alport syndrome was ensured by genetic testing.

The large Phase 3 BEACON study (Study 0903), recruiting over 2,000 subjects with Type 2 diabetes (T2DM) and stage 4 CKD (eGFR ≥ 15 to < 30 mL/min/1.73 m^2), was terminated early for safety reasons, as emerging data indicated an increased reporting of events of cardiac congestion and cardiac failure in the bardoxolone arm compared to placebo. It was concluded that the BEACON population represented a high-risk population for cardiovascular events by combining T2DM and severe chronic renal disease, and the clinical development program for T2DM is currently paused.

Subjects with Alport syndrome was considered to represent a population with lower risk for cardiovascular events than the T2DM population, due both to the lack of the inherent cardiovascular morbidity associated with T2DM and to the lower mean age in the Alport target population caused by the early progression to ESRD. To further reduce the potential for bardoxolone-induced fluid overload, exclusion criteria regarding renal and cardiac function were applied to both phases of Study 1603.

The cardiac exclusion criteria are discussed in the safety section.

Subjects with CKD 4-5 (eGFR <30 mL/min/1.73 m2) were excluded from Study 1603 for safety reasons; however, the proposed indication includes all stages of renal function. No justification has been provided for the safe use in subjects with CKD 4-5 (eGFR <30 mL/min/1.73 m2) in Alport syndrome. Furthermore, medicinal products intended to prevent development/slow progression of chronic renal insufficiency generally tend to be less effective in subjects with severe compared to mild-moderate renal dysfunction due to increasing irreversible damage to the renal parenchyma, e.g., fibrosis and atrophy. Extrapolation of efficacy data from the study population therefore needs to be justified. In this context it is noted that in the subgroup analysis (see under Efficacy data and additional analyses), subjects with baseline eGFR ≤60 mL/min/1.73 m2 showed poorer results compared to subjects with baseline eGFR >60 mL/min/1.73 m2. The applicant is requested to justify the use of bardoxolone in subjects with severe renal disease corresponding to CKD 4-5 (eGFR <30 mL/min/1.73 m2), taking both safety and efficacy into consideration, or to reflect the limitations of the study population in the wording of the indication.

Due to the broad renal eligibility criteria (baseline eGFR 30-90 mL/min/1.73 m^2 and UACR <3500 mg/g) and the eligibility for subjects with all subtypes of Alport Syndrome, there is a marked heterogenicity within the treatment arms. In this context, the lifetime risk of ESRD with gender and different Alport subtype is of interest. In summary, the study population spans from subjects with baseline eGFR of 30 mL/min/1.73 m^2 and an Alport subtype with 100% lifetime risk of ESRD to subjects with 90 mL/min/1.73 m^2 and an Alport subtype with 20% lifetime risk of ESRD. However, the point estimate favoured bardoxolone for all prespecified subgroups.

Of note, in both phases, a small number of subjects were included in the study on a waiver despite eGFR outside the broad eligibility criteria of 30-90 mL/min/1.73 m2. This has not been explained. The applicant is asked to clarify the use of a waiver to include subjects with eGFR outside the eligibility criteria**.**

As the inclusion criteria do not define the lower threshold of baseline UACR (ie. patients with a normal UACR value of <30mg/g could be enrolled), it is important to establish that the bardoxolone and placebo group did not differ substantially in the distribution of baseline UACR values. In addition to already presented data (Table 14 in the CSR), the applicant is asked to present the categorical

distribution of baseline UACR values in the following categories: <30 mg/g; ≥30 and <300 mg/g; ≥300 mg/g in both treatment arms. Numbers and percentages of subjects with UACR <30 mg/g per treatment arm and subgroup analyses for the primary efficacy outcome for these patients should be presented. Additionally, the median values of baseline UACR should be reported for both treatment arms.

Requirements for receiving ACEi/ARBs in the study inclusion criteria were changed two times. In Protocol version 2 patients receiving ACEi/ARBs at maximally tolerated labelled daily dose, unless contraindicated, were eligible to enrol in the study. In Protocol version 3 patients in whom ACEi/ARBs were not indicated were also eligible to enrol in the study. The applicant should explain the effect of these protocol changes on the study population given that patients who are not indicated to take ACEi or ARB might have milder disease than patients who are on therapy.

The applicant is asked to address the issue of representativeness of EU population, whether Alport syndrome studied paediatric population could be extrapolated to the EU-population, and to discuss discrepancies in baseline renal function indicators among paediatric population enrolled in Alport syndrome safety pool.

Statistical considerations

Study 1603/Phase 3

In the primary and secondary analyses, eGFR collected after starting dialysis or after receiving a kidney transplant is considered invalid and is treated as missing and the primary analysis of efficacy is based on an assumption of missing at random (MAR). This approach is not accepted. Starting dialysis or receiving a kidney transplant is an indication of a permanently failed kidney function and values after such event should be imputed with a worst possible score (e.g., 5 mL/min/1.73m^2)**.**

1603/Phase 2 and the first 76 weeks of 1603/Phase 3 were completed before the start of the COVID19 pandemic. After Week 76 in 1603/Phase 3, approx. 20% of all visits were impacted by COVID-19. More visits in the placebo arm compared to the bardoxolone arm were affect, e.g., 26% versus 21% of the visits at Week 100 (primary endpoint). Values collected after the start date of adverse event preferred term "coronavirus" has been excluded from analysis. Although an assumption of MAR is more plausible in this case, a sensitivity analysis including all such values should be provided for primary and key secondary endpoints.

The inclusion of fraction of 1-year/2-year exposure to treatment as covariate in the primary analysis of the primary and secondary endpoints is not in line with the EMA Guideline EMA/CHMP/295050/2013 *Adjustment for baseline covariates in clinical trials* since it could be affected by the allocated treatment. As stated in the guideline: "*When a covariate is affected by the treatment either through direct causation or through association with another factor, the adjustment may hide or exaggerate the treatment effect"*. Hence all analyses of primary and secondary endpoints should be repeated both including and excluding this covariate (both original analysis and analysis with imputations mentioned above).

The method to protect the overall type I error as presented above is considered acceptable. However, in the study report, it is stated that "*Because both Year 1 endpoints in the testing sequence were statistically significant at a level of 0.025, 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, the Year 2 testing sequence used a significance level of 0.05.*" Although, this procedure per se could be acceptable, it was not prespecified in the protocol or SAP and hence is not accepted. There are a number of ways to recycle alpha in this study and the way to be used needs to be specified in advance. Hence all p-values for year 2 testing should be interpreted against the prespecified alpha level of 0.025 and all confidence intervals should be presented as 97.5%, both for primary- and sensitivity analyses.

Furthermore, the tipping point analysis for year 2 should be repeated with the 0.025 level of significance.

Study 1603/Phase 2

Only on-treatment data were included in the primary analysis. Although this can be accepted in a phase 2 trial, it usually biases the estimate towards a larger effect compared with a treatment policy analysis. As this was a single arm trial, statistical inference was based on change from baseline and must be interpreted with care.

Whether eGFR collected after starting dialysis or after receiving a kidney transplant was included in the analysis is not clear and should be clarified. If such values were excluded from analysis, new analysis with a worst-case imputation should be provided.

Efficacy data and additional analyses

Patient disposition

Between August 2017 and November 2018, 371 subjects were screened, of which a very large number were excluded (n=214). The vast majority of excluded subjects failed to meet inclusion criteria (184 subjects). Hence, the generalisability of the study results is questionable based on the fact that over 50% of potentially eligible patients were not suitable for inclusion in this single pivotal trial. The applicant is invited to discuss generalisability in face of these exclusions.

In Study 1603/Phase 3, 157 subjects were enrolled. Of these, 80 subjects received placebo and 77 subjects received bardoxolone.
More subjects in the bardoxolone arm compared to the placebo arm (17/77 and 9/80, respectively), discontinued study treatment before Week 48. In total, 51/77 subjects (66%) of the subjects in the bardoxolone arm and 67/80 (84%) of the subjects in the placebo arm completed treatment through Week 100 and had a Week 104 study visit of the 1603/Phase 3 cohort. The difference between the treatment arms was driven primarily by more discontinuations in Year 1 of the study due to protocol-specified withdrawal criteria (6 [7.8%] in the bardoxolone methyl group and none in the placebo group) and AEs (8 [10.4%] in the bardoxolone methyl group and 4 [5.0%] in the placebo group). The applicant is asked to clarify which protocol-specified withdrawal criteria led to discontinuation.

Furthermore, the applicant should present discontinuations over time in the form of Kaplan-Meier curves for each treatment arm, for both discontinuation of treatment and discontinuation of study.

In the 1603/Phase 2 cohort, 30 subjects were enrolled. All subjects were still on treatment at the primary analysis at Week 12. At Week 104, 7/30 (23%) had discontinued study treatment. 24/30 (80%) of the subjects completed the 1603/Phase 2.

Nine patients were reported with end stage renal disease. Of these, three subjects received placebo in Study 1603/Phase 3, and six subjects (three in each study) received bardoxolone methyl. In two cases (one placebo, one bardoxolone), study treatment was terminated before the event of ESRD. These cases, unlike the remaining seven cases, were not reported as TEAE. In six of the seven cases with ongoing treatment, the event of ESRD led to drug withdrawal. In the last case, no action was taken with study treatment. All subjects had baseline eGFR in the lower spectrum (27-41 mL/min/1.73 m2) and high baseline UACR (882-2207 mg/g), both factors representing a high risk for disease progression.

The higher proportion of patients from Phase 2 compared to Phase 3 progressing to ESRD requires clarification. The applicant should: a) confirm that all 3 patients progressing to ESRD in Phase 2 were included in analyses at Week 12 and analyses at all subsequent timepoints; b) confirm that all patients

progressing to ESRD in Phase 3 trial (3 in bardoxolon and 3 in placebo) were included in analyses at all timepoints; c) should confirm that all cases of ESRD have been identified and reported and should present new cases of ESRD (other than the 9 mentioned above) if applicable and d) discuss the larger proportion of patients from Phase 2 study progressing to ESRD compared to patients from Phase 3 progressing to ESRD. The progression to ESRD observed in Phase 2 cohort during treatment with bardoxolon is concerning and requires further elucidation.

Baseline data

In the 1603/Phase 3 cohort, mean age and mean baseline eGFR were balanced between the treatment arms (39.6 versus 38.8 years and 62.6 versus 62.7 mL/min/1.73 m2 for placebo and bardoxolone, respectively). A similar proportion of the subjects in each treatment arm had the X-linked form of Alport syndrome (51/80 [63.8%] in the placebo arm vs 47 [61.0%] in the bardoxolone arm).

In regard to baseline ACEi/ARB status, 25.0% of patients in the placebo group and 19.5% of patients in the bardoxolone methyl group were not taking either of these medications. Patients who are not indicated to take ACEi or ARB might have milder disease than patients who are on therapy. The applicant should provide information on reasons for these patients not being on ACEi or ARB therapy and include the information on baseline eGFR, proteinuria and haematuria for these patients.

Patients in the placebo group more frequently reported immune system disorders, musculoskeletal and connective tissue disorders, respiratory, thoracic and mediastinal disorders and social circumstances disorders in their medical history compared to bardoxolone group patients. Bardoxolone group patients more frequently reported ear and labyrinth disorders and vascular disorders compared to placebo group. It appears that patients in placebo group had higher burden of concomitant diseases than patients in bardoxolone group. The applicant is asked to discuss whether these imbalances could have had an effect on study outcomes.

Taken together, there were no major imbalances between the two treatment arms expected to have impact on study outcome.

The paediatric subgroup was small with 12 subjects <18 years in the placebo arm and 11 subjects in the bardoxolone arm, leading to somewhat larger imbalances between the treatment arms. Age and baseline eGFR were balanced (15.2 versus 15.4 years and 68.2 versus 71.9 mL/min/1.75 m2 for placebo and bardoxolone respectively).

Adolescent subpopulation was well balanced between treatment arms with respect to baseline eGFR values with most of the subjects (10/12 in placebo group and 9/11 in bardoxolone methyl group) in >60mL/min/1,73m2 category. However, regarding baseline UACR, subjects in bardoxolone methyl group had disproportionally higher geometric mean UACR values vs placebo (bardoxolone methyl group:409,35; SE 187.045 vs placebo: 136,59; SE 89.974) which can indicate that there were discrepancies between groups when it comes to disease progression. The applicant is asked to comment on these differences.

Change in eGFR from baseline at Week 48 and Week 100.

The primary endpoint in Study 1603/Phase 3 was the Change from Baseline in eGFR at Week 48 and Week 100. The Week 100 endpoint was amended to meet the concern from CHMP in the protocol assistance procedure (EMA/CHMP/SAWP/599796/2018) that the Week 48 analysis may be too early and carry a risk of overestimating the benefit of the compound. This amendment is supported. The use of change in eGFR from baseline and not time to a predefined and justified loss in GFR, such as 50%, as proposed by the CHMP was justified by the outcome of the National Kidney Foundation (NKF) sponsored workshop conducted in collaboration with the FDA and EMA in March 2018. This is accepted.

These end points are less applicable at higher baseline GFRs and in the context of agents that cause an "acute effect" on GFR decline (an early treatment effect of the intervention that differs from the later treatment effect), making them less practical for drugs targeted at earlier stages of kidney disease and drugs with potential hemodynamic effects. Surmounting these limitations may involve examining changes in albuminuria (or proteinuria) as an earlier marker of kidney disease progression, assessing the rate of GFR decline (slope), and combined use of both these approaches. In Study 1603 Phase 2/3, assessment of the slope of eGFR decline beyond Week 48 is however not possible due to the two off-treatment periods Week 48-52 and Week 100-104.

At Week 48 in the 1603/Phase 3 cohort, the change from baseline (LS mean) in eGFR in the placebo arm was -4.77 mL/min/1.73 m2 compared to +4.71 mL/min /1.73 m2 in the bardoxolone arm, yielding an LS mean difference between the treatment arms of 9.49 mL/min/1.73 m2 ($p<0.0001$). The corresponding number for Week 100 was -8.45 mL/min/1.73m2 for the placebo arm and -0.81 mL/min/1.73 m2 for the bardoxolone arm, yielding a difference of 7.65 mL/min/1.73 m2 ($p=0.0005$). Thus, Study 1603/Phase 3 met its primary endpoint.

Although the primary analysis is based on the ITT population, a considerable number of subjects seems to be excluded from analysis (20 subjects in the w48 analysis and 19 subjects in the w100 analysis). This should be clarified and if this is the case, a new analysis including all subjects should be provided with necessary imputation.

A prespecified subgroup analysis was performed for the primary analysis at Week 100. The subgroups analysed included age (<18, ≥18 years), gender, baseline UACR (≤300 mg/g, >300 mg/g), use of RAAS inhibition and baseline eGFR ≤ 60, >60 mL/min/1.73 m^2) and genetic subtype (XLAS, non-XLAS). In all subgroups, the point estimate favours bardoxolone, although not always significantly. Of note, subjects with baseline eGFR ≤60 mL/min/1.73 m^2 showed markedly poorer results compared to subjects with baseline eGFR >60 mL/min/1.73 m^2 with placebo-corrected difference from baseline of 2.5 mL/min/1.73m^2 (N=58; p=0.44) and 11.4 mL/min/1.73m^2 (N=80; p<0.0001), respectively. In fact, the subgroup of subjects with baseline eGFR ≤60 mL/min/1.73 m^2 had the poorest effect of all subgroups analysed.

eGFR change from baseline at Week 48 and Week 100 was secondary endpoint in the 1603/Phase 2 cohort. The results were consistent with these in the 1603/Phase 3 cohort. Data from supportive studies in CKD from other conditions were provided. Taken together, a positive effect on eGFR at Week 48 has been shown.

Change in eGFR from baseline at Week 52 and Week 104.

Change from Baseline in eGFR at Week 52 and Week 104 after four weeks off treatment was the key secondary endpoint in Study 1603/Phase 3.

To address the concern that the treatment effect was due to an increase in intraglomerular pressure which would be detrimental for disease progress the applicant has included the two four-week off treatment periods after Week 48 and Week 100 respectively. According to the applicant, non-clinical data indicate that bardoxolone methyl produces acute increases in eGFR by increasing glomerular surface area and by reversing endothelial dysfunction and mesangial cell contraction, restoring GFR of individual nephrons without changes in intraglomerular pressure (pending responses to the LoQ where additional clarifications are requested), but these data need clinical confirmation. Therefore, the off-treatment periods were added to the protocol. The applicant has provided an extensive justification for the length of the four-week off-treatment periods. The data provided in support are limited and with high variability, hampering the precision of the diminishing of the acute effect. There are however indications that the 30 days off-treatment may not be sufficient for a complete washout of pharmacodynamic effects. Of note, the visit window for the Week 52 and Week 104 analyses was

broad, allowing test sampling after as little as two weeks off treatment. The purpose of the analysis of the secondary endpoints based on week 52 and week 104 data was to examine any remaining effect after 4 weeks of treatment discontinuation. Hence a supplementary analysis should be performed on observed values without imputation including only values at least 4 weeks after last dose of study treatment.

The data presented in section 5.1 of the SmPC are placebo corrected, showing an LS Mean difference between the treatment arms of 5.1 mL/min/1.73 m^2 at Week 52 (p=0.0021) and of 4.3 mL/min/1.73 m2 at Week 104 (p=0.0232). Although correct, this is considered somewhat problematic. While the slope of the placebo arm is generally constant or flattened during the off-treatment windows (change from baseline -4.77 mL/min/1.73 m^2 Week 48 versus -6.08 mL/min/1.73 m^2 Week 52 and -8.45 mL/min/1.73 m^2 Week 100 versus -8.84 mL/min/1.73 m^2 Week 104), the slope is clearly steepened during off-treatment in the bardoxolone arm (change from baseline +4.71 mL/min/1.73 m2 Week 48 versus -0.99 mL/min/1.73 m^2 Week 52 and -0.99 mL/min/1.73 m^2 Week 100 versus -4.52 mL/min/1.73 m^2 Week 104). This should be reflected in the SmPC by adding a figure showing eGFR over time from Week 0 to Week 104.

Off treatment data from the 1603/Phase 2 cohort, the extension study 1803 and the two diabetes studies 0804 and 0903 are consistent with the findings from the Phase 3 cohort. However, Change from Baseline (CFB) in eGFR at Week 52 and Week 104 (an exploratory endpoint in the 1603/Phase 2 study performed on the per protocol population) were less favourable for bardoxolone compared to on-treatment analyses. When comparing CFB in the PP population at Week 48 and Week 52, a difference of -6.63 mL/min/1.73 m2 is observed. Similarly, when comparing CFB in the PP population at Week 100 and Week 104, a difference of -11.95 mL/min/1.73 m2 is observed. This would translate into a decline in eGFR after treatment with bardoxolone is stopped, with a more pronounced decline if the treatment duration was longer. The applicant should discuss these findings.

At the fourteenth DMC quarterly data review teleconference on September 1, 2020, DMC requested further analyses to better understand the trajectory of estimated glomerular filtration rate (eGFR) over time for patients based on treatment status. The DMC requested to review observed eGFR data only, and that off-treatment values in patients who discontinued is not to be carried forward.
The applicant should present sensitivity analyses in line with the analyses requested at the fourteenth DMC quarterly data review teleconference on September 1 2020 (i.e. observed eGFR values at each study visit and CFB through the last study visit; observed eGFR using on-treatment data [any data collected after treatment discontinuation is excluded] and their CFB; eGFR using all observed values for patients who discontinued treatment and their CFB).

Continuous eGFR (eGFR Over Time)

Continuous eGFR (eGFR Over Time) was an exploratory efficacy analysis in Study 1603/Phase 3. However, the results are considered of interest for the interpretation of efficacy in the study.

In the Alport studies, eGFR improved rapidly compared to baseline during the first approximately 12 weeks of bardoxolone treatment. As adequately pointed out by the applicant, clinical conditions or treatment-related increases in eGFR are conventionally thought to be caused by an increase in intraglomerular pressure, which could lead to accelerated damage to the glomeruli and accelerated progression to ESRD. To address this, the applicant has conducted studies to characterise bardoxolone methyl's mechanism for increasing GFR in a non-clinical setting. According to the applicant, these data, together with reports from the scientific literature, indicate that bardoxolone methyl produces acute increases in eGFR by increasing glomerular surface area and by reversing endothelial dysfunction and mesangial cell contraction, thus restoring GFR of individual nephrons without changes in intraglomerular pressure. Clarifying questions on these novel mechanisms are raised elsewhere**.**

After the initial improvement, eGFR in the bardoxolone arm falls from Week 12 to Week 48 at a rate visually not largely differing from that in the placebo arm in the 1603/Phase 3 study. Furthermore, there was a rapid decline in eGFR at treatment withdrawal. The available data is not indicative of a disease modifying effect, but rather that t the major benefit with bardoxolone treatment is the rapid pharmacodynamic effects. A treatment transiently increasing renal function could under some circumstances be beneficial without an accompanying shift in long-term progression rate. Delaying the need of dialysis and/or renal transplantation even with as little as one or two years could be of importance to the patients. However, the applicant should present a discussion regarding clinical relevance of the observed transient (i.e., steep decrease in eGFR after treatment withdrawal) rise in eGFR.

Notwithstanding, few patients have been exposed to longer treatment periods than two years, and although the slopes appear parallel during the placebo-controlled period, there are scarce data available to exclude more rapid deterioration of GFR over time. Of note, in non-clinical study RTA-P-19006 in mice, there are strong indications of renal toxicity. A question on the kidney findings in the non-clinical setting has been raised**.** The applicant claims that the toxicity in rodents is caused by a rodent-specific metabolism. The metabolism in humans and potential occurrence of (toxic) metabolites is not fully elucidate. In this context, it is also noted that bardoxolone treatment was related to an increase in the urine albumin creatinine ratio (UACR). It is agreed with the applicant that an increase in glomerular filtration could lead to an increase in albuminuria. Notwithstanding, in such case, the excretion of creatinine is expected to raise in parallel. Albumin excretion is a well described surrogate marker for glomerular damage. This needs further discussion
The applicant should present further long-term data as available and discuss the possibility of detrimental long-term effect of treatment. In this context possible rebound effects upon treatment cessation should be discussed. Furthermore, the applicant should discuss whether a direct effect of bardoxolone on the podocytes resulting in an alteration in the filtration barrier can be excluded. The applicant is also asked to discuss whether an increase in UACR has been reported in other products intended for renoprotection. Furthermore, the development of UACR after discontinuation of bardoxolone should also be discussed**.**

Study protocol version 3 (30 July 2018) introduced the time-to-first kidney failure outcome event as a composite exploratory endpoint. In protocol version 4 (22 April 2019) Year 1 endpoint design was changed from time-to-event analysis to assessment of the percentage of bardoxolone methyl-treated patients relative to placebo with a kidney failure event. Year 2 endpoint remained as time-to-event analysis. The composite outcome includes individual components of unequal clinical significance (ESKD, eGFR <15 mL/min/1,73 m2 and 30% decline from baseline in eGFR). The difference between the two treatment arms is driven by the difference in the least clinically relevant outcome (30% decline in eGFR), while there is no difference in other, more clinically relevant components of this outcome. Progression to ESKD was observed in 3 patients in placebo and 3 patients in bardoxolone groups, while eGFR <15 was observed in 3 patients in placebo and 2 in bardoxolone arms. The applicant should discuss the relevance of 30% decline from baseline in eGFR in describing kidney failure event, especially considering very broad baseline eGFRs in study population.

Mean time to kidney failure composite event for the placebo group is 89.21 (SE 2.894) weeks, and for the bardoxolone methyl group is 62.52 (SE 1.049) weeks. Analysis of time to First Kidney Failure Event shows lack of a statistically significant difference between patients treated with placebo and bardoxolone (HR 0.493 (95% CI 0.2, 1.1; p=0.0864). It seems that kidney failure outcomes occur approximately 27 weeks earlier in patients on treatment and it might imply that bardoxolone methyl causes faster deterioration of renal function, especially in patients with already poor parameters of kidney function (low baseline eGFR and high baseline UACR). The applicant should provide a discussion on this issue.

Assessment of paediatric data on clinical efficacy

Study 1603/Phase 3 included 12 subjects aged 12-<18 years in the placebo arm and 11 subjects in the bardoxolone arm.

The paediatric population in Study 1603/Phase 3 had a mean baseline eGFR values of approximately 70 mL/min/1.73 m^2. The paediatric subpopulation had the largest annual rates of eGFR decline prior to study entry (-11 mL/min/1.73 m^2 per year). Treatment with bardoxolone methyl resulted in a decrease from baseline in eGFR of 1.4 mL/min/1.73 m^2 at Week 100, while treatment with placebo resulted in a decrease in eGFR of -15 mL/min/1.73 m^2. At Week 104, following a 4-week off-treatment period, mean changes from baseline in eGFR -2.9 mL/min/1.73 m^2 for bardoxolone methyl-treated paediatric patients and -18 mL/min/1.73 m^2 for placebo-treated paediatric patients.
In summary, there was no indication of a poorer response to bardoxolone in the limited paediatric efficacy population.

The popPK analysis results show that age is not a statistically significant predictor for bardoxolone pharmacokinetics.

However, further detail of exposure vs body weight in support of the dosing recommendation for adolescents as well as a discussion of a potential weight restriction, knowing that no information on bardoxolone PK in subjects below 46 kg is available, is requested.

3.3.6. Conclusions on clinical efficacy

Study 1603/Phase 3 met its primary and secondary endpoint. However, the possibility of detrimental long-term effect of bardoxolone treatment and possible rebound effects upon treatment cessation needs further discussion. A discussion regarding clinical relevance of the observed transient rise in eGFR is requested. Furthermore, the proposed indication is broad and includes all stages of renal function in Alport syndrome. It is questioned that a positive benefit/risk ratio has been shown for the entire target population.

Concerns about study conduct in light of unblinding od the Sponsor midway through the trial, poor communication with stakeholders during the trial, failure to re-consent patients, overall DMC concerns, extensive protocol changes and frequent major protocol deviations including the informed consent need to be further addressed.

In addition, there is a number of other concerns in need of clarifications as detailed in the discussion above and in the LoQ.

3.3.7. Clinical safety

Bardoxolone has been investigated in 3 studies on Alport syndrome. The randomized phase 3 Cardinal study (402-C-1603/Phase 3) is the pivotal study where 150 patients (77 Bardoxolone/80 placebo) were studied for 104 weeks. The Cardinal study also involved a preceding phase 2 single arm part where 30 patients were studied for 104 weeks (402-C-1603/Phase 2). The EAGLE study (402-C-1803) is an ongoing open-label extended access phase 3a study in which 96 patients with Alport syndrome is currently enrolled. The EAGLE study was open to subjects from the two phases of the Cardinal study only.

The Alport syndrome participants were exposed to bardoxolone according to the proposed titration dosing regimen up to 20-30 mg once daily (based on baseline UACR) and were exposed to the proposed commercial formulation of the medicinal product.

Bardoxolone has been extensively investigated in different clinical settings (2 Phase 3 studies and 11 Phase 2 studies in type 2 diabetes CKD, rare CKD, pulmonary hypertension, pancreatic cancer) with different bardoxolone formulation and dosing regimens. The applicant has divided the data into 4 different analysis sets based on study type and the studied conditions.

Analysis set A consists of the pivotal placebo-controlled study in patients with Alport syndrome (i.e., 1603/phase 3) whereas analysis set B contains safety data from two additional uncontrolled studies (1603/Phase 2 and 1803).

Analysis set C consists of placebo-controlled studies in CKD (i.e., the pivotal RCT on Alport syndrome and two additional RCTs on T2DM and CKD) whereas analysis set D also contains data from single-armed studies and studies on other diseases.

The safety results presented in the SCS mainly focuses on the safety analysis sets A and B which is acknowledged. However, analysis set C has a value for assessment of more rare side effects of bardoxolone, given the larger number of patients included.

Analysis set D is only briefly discussed given that the included studies differ in design and length and also includes patients with pulmonary arterial hypertension.

3.3.7.1. Patient exposure

In total, 153 patients have been exposed to bardoxolone in the proposed indication (30 patients from Study 1603 Phase 2, 77 patients from Study 1603 Phase 3 and 46 patients who previously received placebo in Study 1603 Phase 3 and were subsequently included in the open-label extension Study 1803). In addition, 1230 subjects have been exposed to bardoxolone in CKD and T2D. The median duration of exposure in subject in the proposed indication (Analysis set B) is 1.68 years (0.0-3.2yrs). In total, 106/153 (70%) of the subjects were treated for at least 6 months and 88/153 (75.5%) for 12 months. 53 of the 153 subjects (35%) were treated for > 96 weeks.

In total the extent of exposure in the proposed indication is low. However, considering a rare disease, the exposure is considered acceptable.

In Analysis set A, i.e., the pivotal study, the median treatment duration in the bardoxolone and placebo groups were in the same range (1.77 y and 1.83 y). 73% of patients in the bardoxolone group took the medication for more than 48 weeks compared to 85% in the placebo group. The reason for shorter treatment duration in the bardoxolone group is early withdrawal from treatment due to "Protocol-Specified Withdrawal Criterion Met". The applicant is asked to clarify which protocol-specified withdrawal criteria led to discontinuation.

Analysis set B encompasses some patients with longer exposure (max 3.2 y) from the long-term extension (that included patients who completed either study 1603 phase 3 or 1603 phase 2). 57.5% of patients took the medication for more than 48 weeks. In analysis set B, the cumulative exposure was 221.5 patient years in the bardoxolone group from and 126.8 years in the placebo group.

The placebo group is the same population in analysis set A and B. Some caution needs to be taken when comparing bardoxolone data from analysis set B with the placebo group due to the added single arm data in analysis set B where reporting of AEs may be different than during the RCT. Also, reporting in patients from the long-term extension may differ given that patients transferred from previous studies.

Analysis set C included the pivotal RCT in Alport patients and two RCTs in patients with CKD and T2D. In total, this set includes 1230 patients treated with bardoxolone for a median of 0.52 y and 1232 patients on placebo for median 0.62 y.

The proposed indication covers adolescents (12-18 y). In total 21 subjects <18 years have been exposed to bardoxolone methyl with a median age of 15 (13-17) years. Of paediatric patients in analysis set B, 11 (55.0%) were exposed for >48 weeks, and 7 (35.0%) for >96 weeks.

3.3.7.2. Adverse events

The TEAE profiles for the overall population and the paediatric patients are summarized in Table 28, and in Table 29, respectively.

Table 28. Overall Summary of Treatment-Emergent Adverse Events (Analysis Set A and Analysis Set B).

	Analysis Set A				Analysis Set B		
	Bardoxolone Methyl			Placebo	Bardoxolone Methyl		
	20 mg (N = 42)	30 mg (N = 35)	Combined (N = 77)	(N = 80)	20 mg (N = 89)	30 mg (N = 75)	Combined (N = 153)
Number (%) patients with TEAE	40 (95.2%)	35 (100%)	75 (97.4%)	77 (96.3%)	83 (93.3%)	71 (94.7%)	146 (95.4%)
TEAE Related to Study Drug	38 (90.5%)	32 (91.4%)	70 (90.9%)	45 (56.3%)	70 (78.7%)	61 (81.3%)	125 (81.7%)
TEAE with Action Taken of Study Drug Interrupted	12 (28.6%)	11 (31.4%)	23 (29.9%)	13 (16.3%)	28 (31.5%)	22 (29.3%)	50 (32.7%)
TEAE with Action Taken of Study Drug Discontinued	8 (19.0%)	9 (25.7%)	17 (22.1%)	4 (5.0%)	8 (9.0%)	12 (16.0%)	20 (13.1%)
Serious TEAE	1 (2.4%)	7 (20.0%)	8 (10.4%)	15 (18.8%)	3 (3.4%)	13 (17.3%)	16 (10.5%)
Serious TEAE Related to Study Drug	1 (2.4%)	0	1 (1.3%)	1 (1.3%)	1 (1.1%)	0	1 (0.7%)
TEAE with Severity							
Mild	15 (35.7%)	6 (17.1%)	21 (27.3%)	26 (32.5%)	31 (34.8%)	15 (20.0%)	44 (28.8%)
Moderate	24 (57.1%)	21 (60.0%)	45 (58.4%)	42 (52.5%)	46 (51.7%)	42 (56.0%)	85 (55.6%)
Severe	1 (2.4%)	8 (22.9%)	9 (11.7%)	9 (11.3%)	6 (6.7%)	14 (18.7%)	20 (13.1%)
TEAE Related to Study Drug with Severity							
Mild	18 (42.9%)	13 (37.1%)	31 (40.3%)	26 (32.5%)	30 (33.7%)	26 (34.7%)	55 (35.9%)
Moderate	19 (45.2%)	13 (37.1%)	32 (41.6%)	16 (20.0%)	35 (39.3%)	27 (36.0%)	60 (39.2%)
Severe	1 (2.4%)	6 (17.1%)	7 (9.1%)	3 (3.8%)	5 (5.6%)	8 (10.7%)	13 (8.5%)
Patients Who Had a Fatal TEAE	0	0	0	0	0	0	0

Abbreviation: TEAE=treatment-emergent adverse event
Note: For counts by severity, patients with multiple events are counted only once at the highest severity.
Source: ISS Table 7.1.1; ISS Table 7.1.2

Table 29. Overall Summary of Treatment-Emergent Adverse Events (Analysis Set A and Analysis Set B) in Paediatric Patients

	Analysis Set A		Analysis Set B
	Bardoxolone Methyl (N = 11)	Placebo (N = 12)	Bardoxolone Methyl (N = 20)
Patients Who Had a TEAE	11 (100%)	10 (83.3%)	18 (90.0%)
Patients Who Had a TEAE Related to Study Drug	11 (100%)	4 (33.3%)	15 (75.0%)
Patients Who Had a TEAE with Action Taken of Study Drug Interrupted	4 (36.4%)	2 (16.7%)	6 (30.0%)
Patients Who Had a TEAE with Action Taken of Study Drug Discontinued	1 (9.1%)	1 (8.3%)	1 (5.0%)
Patients Who Had a Serious TEAE	0	2 (16.7%)	0
Patients Who Had a Serious TEAE Related to Study Drug	0	0	0
Patients Who Had a TEAE With Severity of			
Mild	3 (27.3%)	4 (33.3%)	5 (25.0%)
Moderate	8 (72.7%)	5 (41.7%)	12 (60.0%)
Severe	0	1 (8.3%)	1 (5.0%)
Patients Who Had a TEAE Related to Study Drug with Severity of			
Mild	8 (72.7%)	2 (16.7%)	10 (50.0%)
Moderate	3 (27.3%)	2 (16.7%)	5 (25.0%)
Severe	0	0	0
Patients Who Had a Fatal TEAE	0	0	0

Abbreviation: TEAE=treatment-emergent adverse event
Note: For counts by severity, patients with multiple events are counted only once at the highest severity.
Source: ISS Table 7.1.1.1.9; ISS Table 7.1.2.1.9

In the pivotal study (1603/phase 3 [analysis set A]) almost all subjects reported any TEAE in both the bardoxolone (97%) and the placebo group (96%). However, TEAEs related to study drug was more common in the bardoxolone group compared to the placebo group (91% vs 56%). TEAEs with action taken to study drug discontinuation were more common in the bardoxolone group (22%) compared to the placebo group (5%).

Serious TEAEs (SAEs) were reported less frequently in the bardoxolone group (10.4 %) for the combined dose groups than placebo (18.8%). There were very few cases of SAEs deemed as related to the study drug across the groups.

No fatal TEAEs was reported in any of the two (A and B) analysis groups.

Overall, no major differences were noted when comparing analysis set A and B regarding overall safety.

Among the SOCs, higher frequency of AEs for bardoxolone vs. placebo was observed in the SOC investigations, gastrointestinal disorders, respiratory, thoracic and mediastinal disorders.

Lower frequency of AEs in the bardoxolone group was observed in nervous system disorders, psychiatric disorders, ear and labyrinth disorders, eye disorders and hearing and vestibular disorders. These AEs may be related to common non-kidney manifestations of Alport disease; thus, the decreased incidence may be related to the treatment effect.

Results were similar for the paediatric patients. There were however no serious TEAEs in this group and TEAEs were in general less severe. The precision of the estimate is however limited by the low number of paediatric participants in the study.

Serious and severe TEAEs and TEAEs with action taken of study drug discontinued tended to be more frequent in the higher bardoxolone dose group.

Common adverse events

The common TEAEs from the pivotal study and analysis B are presented in Table 30. Listings of TEAEs occurring in ≥10% of bardoxolone treated patients and with a difference in incidence of ≥2% vs placebo have been provided. The applicant is asked to present an overall tabulation on all PTs organized by SOC reported with a frequency ≥1% in any treatment arm.

TEAEs in the paediatric population are summarized in Table 31. TEAEs from analysis set C are provided in Table 32

Table 30. Summary of Treatment-Emergent Adverse Events Occurring in ⩾10% of Bardoxolone Treated Patients and With a Difference in Incidence of ⩾2% vs Placebo in Analysis Set A (Analysis Set A and Analysis Set B)

	Analysis Set A				Analysis Set B		
System Organ Class / Preferred Term	Bardoxolone Methyl			Placebo (N = 80)	Bardoxolone Methyl		
	20 mg (N = 42)	30 mg (N = 35)	Combined (N = 77)		20 mg (N = 89)	30 mg (N = 75)	Combined (N = 153)
Musculoskeletal and Connective Tissue Disorders							
Muscle spasms	18 (42.9%)	20 (57.1%)	38 (49.4%)	28 (35.0%)	37 (41.6%)	38 (50.7%)	72 (47.1%)
Investigations							
Alanine aminotransferase increased	22 (52.4%)	14 (40.0%)	36 (46.8%)	1 (1.3%)	40 (44.9%)	25 (33.3%)	65 (42.5%)
Aspartate aminotransferase increased	12 (28.6%)	7 (20.0%)	19 (24.7%)	0	22 (24.7%)	12 (16.0%)	34 (22.2%)
Brain Natriuretic Peptide Increased	4 (9.5%)	6 (17.1%)	10 (13.0%)	3 (3.8%)	10 (11.2%)	9 (12.0%)	19 (12.4%)
Weight decreased	2 (4.8%)	8 (22.9%)	10 (13.0%)	1 (1.3%)	4 (4.5%)	9 (12.0%)	13 (8.5%)
General Disorders and Administration Site Conditions							
Fatigue	7 (16.7%)	7 (20.0%)	14 (18.2%)	12 (15.0%)	11 (12.4%)	14 (18.7%)	25 (16.3%)
Oedema peripheral	6 (14.3%)	6 (17.1%)	12 (15.6%)	10 (12.5%)	11 (12.4%)	11 (14.7%)	22 (14.4%)
Metabolism and Nutrition Disorders							
Hyperkalaemia	3 (7.1%)	8 (22.9%)	11 (14.3%)	5 (6.3%)	11 (12.4%)	18 (24.0%)	29 (19.0%)
Infections and Infestations							
Upper respiratory tract infection	8 (19.0%)	3 (8.6%)	11 (14.3%)	8 (10.0%)	14 (15.7%)	10 (13.3%)	24 (15.7%)
Gastrointestinal Disorders							
Diarrhoea	7 (16.7%)	5 (14.3%)	12 (15.6%)	6 (7.5%)	11 (12.4%)	7 (9.3%)	18 (11.8%)
Respiratory, Thoracic and Mediastinal Disorders							
Cough	3 (7.1%)	5 (14.3%)	8 (10.4%)	3 (3.8%)	5 (5.6%)	7 (9.3%)	12 (7.8%)

Abbreviations: MedDRA=Medical Dictionary for Drug Regulatory Affairs; TEAE=treatment-emergent adverse event
Note: Some patients may be represented in multiple columns if they changed treatment or dose level when entering the extension. Each column reflects the number of unique patients. Events are counted within the treatment group at the start of the event.
Note: Selected events are treatment-emergent events that occur in ≥10% of patients in the Bardoxolone Methyl group and have ≥2% higher incidence in the Bardoxolone Methyl group than Placebo group, based on Analysis Set A population.
Note: Adverse event terms were mapped according to MedDRA v21.1.
Source: ISS Table 8.20.1; ISS Table 8.20.2; ISS Table 8.1.2

Table 31. Summary of Treatment-Emergent Adverse Events Occurring in ⩾2 Paediatric Patients in the Combined Bardoxolone Methyl Treatment Group (Analysis Set A and Analysis Set B)

System Organ Class / Preferred Term	Analysis Set A		Analysis Set B
	Bardoxolone Methyl Combined (N=11)	Placebo (N=12)	Bardoxolone Methyl Combined (N=20)
Number (%) of Patients Reporting TEAEs	11 (100%)	10 (83.3%)	18 (90.0%)
Investigations			
Alanine Aminotransferase Increased	4 (36.4%)	0	8 (40.0%)
Aspartate Aminotransferase Increased	1 (9.1%)	0	4 (20.0%)
Blood Creatine Phosphokinase Increased	2 (18.2%)	3 (25.0%)	3 (15.0%)
Coronavirus Test Positive	1 (9.1%)	0	2 (10.0%)
Weight Increased	1 (9.1%)	0	2 (10.0%)
Musculoskeletal and Connective Tissue Disorders			
Muscle Spasms	5 (45.5%)	4 (33.3%)	5 (25.0%)
Metabolism and Nutrition Disorders			
Hyperkalaemia	3 (27.3%)	1 (8.3%)	4 (20.0%)
Fluid Retention	0	0	2 (10.0%)
General Disorders and Administration Site Conditions			
Fatigue	2 (18.2%)	1 (8.3%)	4 (20.0%)
Non-Cardiac Chest Pain	2 (18.2%)	0	2 (10.0%)
Infections and Infestations			
Nasopharyngitis	3 (27.3%)	3 (25.0%)	4 (20.0%)
Upper Respiratory Tract Infection	3 (27.3%)	0	3 (15.0%)
Gastroenteritis	1 (9.1%)	0	2 (10.0%)
Viral Infection	1 (9.1%)	0	2 (10.0%)
Gastrointestinal Disorders			
Abdominal Pain	3 (27.3%)	0	3 (15.0%)
Nausea	3 (27.3%)	0	3 (15.0%)
Diarrhoea	1 (9.1%)	0	2 (10.0%)
Nervous System Disorders			
Headache	3 (27.3%)	2 (16.7%)	4 (20.0%)
Dizziness	2 (18.2%)	2 (16.7%)	2 (10.0%)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	2 (18.2%)	0	3 (15.0%)
Epistaxis	2 (18.2%)	0	2 (10.0%)
Oropharyngeal Pain	1 (9.1%)	2 (16.7%)	2 (10.0%)
Renal and Urinary Disorders			
Proteinuria	1 (9.1%)	0	2 (10.0%)

Abbreviations: TEAE=treatment-emergent adverse event
Note: Some patients may be represented in multiple columns if they changed treatment or dose level when entering the extension. Each column reflects the number of unique patients. Events are counted within the treatment group at the start of the event.
Note: Adverse event terms were mapped according to MedDRA v21.1.
Source: ISS Table 8.1.1.1.9; ISS Table 8.1.2.1.9

Table 32. Summary of Treatment-Emergent Adverse Events Occurring in ⩾10% of Bardoxolone Treated Patients and With a Difference in Incidence of 2% or More in the Bardoxolone Methyl Treatment Group over the Placebo Group (CKD Placebo-Controlled Bardoxolone Methyl Exposure Integrated Analysis Set C)

System Organ Class/ Preferred Term	Bardoxolone Methyl			Placebo
	15/20 mg (N = 1195)	30 mg (N = 35)	Combined (N = 1230)	(N = 1232)
Number (%) of Patients Reporting Selected TEAEs	844 (70.6%)	28 (80.0%)	872 (70.9%)	560 (45.5%)
Musculoskeletal and connective tissue disorders	480 (40.2%)	20 (57.1%)	500 (40.7%)	197 (16.0%)
Muscle spasms	480 (40.2%)	20 (57.1%)	500 (40.7%)	197 (16.0%)
General disorders and administration site conditions	316 (26.4%)	10 (28.6%)	326 (26.5%)	274 (22.2%)
Oedema peripheral	204 (17.1%)	6 (17.1%)	210 (17.1%)	183 (14.9%)
Fatigue	173 (14.5%)	7 (20.0%)	180 (14.6%)	138 (11.2%)
Metabolism and nutrition disorders	368 (30.8%)	4 (11.4%)	372 (30.2%)	135 (11.0%)
Decreased appetite	210 (17.6%)	3 (8.6%)	213 (17.3%)	87 (7.1%)
Hypomagnesaemia	205 (17.2%)	2 (5.7%)	207 (16.8%)	52 (4.2%)
Gastrointestinal disorders	249 (20.8%)	9 (25.7%)	258 (21.0%)	198 (16.1%)
Nausea	216 (18.1%)	8 (22.9%)	224 (18.2%)	173 (14.0%)
Vomiting	128 (10.7%)	4 (11.4%)	132 (10.7%)	94 (7.6%)
Investigations	223 (18.7%)	8 (22.9%)	231 (18.8%)	44 (3.6%)
Weight decreased	223 (18.7%)	8 (22.9%)	231 (18.8%)	44 (3.6%)

Abbreviations: MedDRA= Medical Dictionary for Drug Regulatory Affairs; TEAE=treatment-emergent adverse event
Note: Adverse event terms were mapped according to MedDRA v21.1.
Source: ISS Table 8.20.3

In the pivotal study 1603/phase 3 (analysis set A), the most reported PT in the bardoxolone treated Alport patients compared to placebo was muscle spasm (49.4% vs. 35.0%) followed by increased ALT (46.7% vs. 2.5%) and increased AST (24.7% vs. 1.3%). Muscle spasm was also frequently observed in the placebo patients while few cases of increased ALT and AST was reported in this group.

In relation to liver biomarkers, the applicant is requested to clarify whether prespecified limit values in the protocol for reporting AEs were provided to the clinical investigators.

Other common PTs reported in higher frequencies (>5%) in the bardoxolone group compared to the placebo group are increases in BNP (13.0% vs. 3.8%), weight decreased (13.0% vs. 1.3%), diarrhoea (15.6% vs. 7.5% placebo), hyperkalaemia (14.3% vs. 6.3%) and cough (10.4% vs. 3.8%).

In analysis set C, encompassing all double-blind, placebo-controlled studies in CKD, an imbalance was also seen for nausea (18.2% vs. 14%) and vomiting (10.7% vs. 7.6%).

There is a discrepancy in the number of events reported for the PTs in the study report from the pivotal study (402-C-1603 PHASE 3, table 38) compared to the numbers given in Analysis set A (Table 30; i.e., Table 18 in the submitted Summary of Clinical Safety). The applicant is requested to clarify.

No clear dose-dependency was seen. This may be due to not all patients reaching their goal dose and that patients dose escalated/de-escalated their dose during the trial.

There was a small increase in oedema peripheral in the bardoxolone treated patients (15.6% in the combined dose groups in analysis set A) vs 12.5% in the placebo group in analysis set A. In analysis set B, the frequency was 14.4%. An imbalance was also seen in analysis set C for this PT (17.1% vs. 14.9%).
Among paediatric Alport syndrome population, commonly observed AEs were similar, except of weight increased, compared to the overall population with somewhat lower incidences of individual AEs. It is acknowledged that conclusions are hampered by small safety pool size. Nevertheless, there were

additional AEs reported in paediatric population (analysis set B): nasopharyngitis (20%), headache (20%), blood CK increased (15%), abdominal pain (15%), weight increased (10%), fluid retention (10%), non-cardiac chest pain (10%), gastroenteritis (10%), viral infection (10%), nausea (15%), dizziness (10%), oropharyngeal pain (10%), proteinuria (10%). Although both muscle spasms and blood CK increased were reported, which can be suggestive of muscle injury, those events were not associated among individuals experiencing muscle spasms.

Adverse Drug Reactions (for inclusion in the Product Information)

The TEAE safety data that met the definition of an ADR were evaluated by the applicant for inclusion as an ADR due to potential clinical significance (i.e., clinically relevant and/or presence of biologic plausibility). TEAEs occurring at a frequency of ≥5% in the bardoxolone group in analysis Set B and with a difference of ≥5% vs the frequency in the placebo group were considered as ADRs (Table 33).

Table 33. Adverse Events Occurring in ⩾5% of Patients in the Bardoxolone Methyl Treatment Group of Analysis Set B with a Difference of ⩾5% vs the Placebo Rate (Analysis Set A and Analysis Set B).

	Analysis Set A		Analysis Set B
Preferred Term	**Bardoxolone Methyl (n = 77)**	**Placebo (n = 80)**	**Bardoxolone Methyl (n = 153)**
Musculoskeletal and Connective Tissue Disorders			
Muscle spasms	38 (49.4%)	28 (35.0%)	72 (47.1%)
Investigations			
Alanine aminotransferase increased	36 (46.8%)	1 (1.3%)	65 (42.5%)
Aspartate aminotransferase increased	19 (24.7%)	0	34 (22.2%)
Brain natriuretic peptide increased	10 (13.0%)	3 (3.8%)	19 (12.4%)
N-Terminal Prohormone Brain Natriuretic Peptide Increased	4 (5.2%)	1 (1.3%)	15 (9.8%)
Weight decreased	10 (13.0%)	1 (1.3%)	13 (8.5%)
Gamma-glutamyltransferase increased	4 (5.2%)	1 (1.3%)	10 (6.5%)
Metabolism and Nutrition Disorders			
Hyperkalemia	11 (14.3%)	5 (6.3%)	29 (19.0%)
Hypomagnesaemia	3 (3.9%)	0	11 (7.2%)
Infections and Infestations			
Upper respiratory tract infection	11 (14.3%)	8 (10.0%)	24 (15.7%)
Respiratory, Thoracic and Mediastinal Disorders			
Epistaxis	7 (9.1%)	0	11 (7.2%)
Skin and Subcutaneous Tissue Disorders			
Alopecia	2 (2.6%)	0	8 (5.2%)

Source: ISS Table 8.1.1; ISS Table 8.15.2

The listed adverse drug reactions in Table 33 are reflected in section 4.8 of the SmPC with appropriate frequencies. However, the determination process and the rationale for selection of ADRs are not agreed upon. An overall tabulation on all PTs organized by SOC reported with a frequency ≥1% in any treatment arm is requested for dataset A and B, respectively. The summary tabulations of adverse reactions should be primarily based on dataset A. Proposed SmPC section 4.8 should be updated accordingly. In addition, a separate table on ADRs in the paediatric population should be considered as

a number of common AEs were reported additionally in that population compared to the overall Alport syndrome population.

Regarding epistaxis, the applicant is requested to discuss the severity of the cases and whether this AE is expected in relation to the mechanism of action pf bardoxolone.

Further EAGLE Study data, beyond the safety database lock date of 18 Jan 2021, together with critical discussion on safety findings are awaited. Please refer to SmPC section 5.1 comment as balanced information is required.

3.3.7.3. Serious adverse events, deaths, and other significant events

A summary of the treatment-emergent SAEs in Alport patients is shown in Table 34. The incidence of Treatment-Emergent Serious Adverse Events by SOC in the BEACON study encompassing patients with CKD stage 4 and T2D is provided in Table 35**.**

Table 34. Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All Alport Set B)

System Organ Class/ Preferred Term	Analysis Set A				Analysis Set B		
	Bardoxolone Methyl			Placebo	Bardoxolone Methyl		
	20 mg (N = 42)	30 mg (N = 35)	Combined (N = 77)	(N = 80)	20 mg (N = 89)	30 mg (N = 75)	Combined (N = 153)
Number (%) of Patients Reporting Serious TEAEs	1 (2.4%)	7 (20.0%)	8 (10.4%)	15 (18.8%)	3 (3.4%)	13 (17.3%)	16 (10.5%)
Renal and Urinary Disorders	1 (2.4%)	3 (8.6%)	4 (5.2%)	3 (3.8%)	1 (1.1%)	6 (8.0%)	7 (4.6%)
End Stage Renal Disease	0	2 (5.7%)	2 (2.6%)	2 (2.5%)	0	5 (6.7%)	5 (3.3%)
Proteinuria	1 (2.4%)	0	1 (1.3%)	1 (1.3%)	1 (1.1%)	0	1 (0.7%)
Acute Kidney Injury	0	1 (2.9%)	1 (1.3%)	0	0	1 (1.3%)	1 (0.7%)
Infections and Infestations	0	0	0	2 (2.5%)	1 (1.1%)	1 (1.3%)	2 (1.3%)
Clostridium Difficile Infection	0	0	0	0	1 (1.1%)	0	1 (0.7%)
Gangrene	0	0	0	0	1 (1.1%)	0	1 (0.7%)
Pneumonia	0	0	0	2 (2.5%)	0	0	0
Pyelonephritis	0	0	0	0	0	1 (1.3%)	1 (0.7%)
Empyema	0	0	0	1 (1.3%)	0	0	0
Injury, Poisoning and Procedural Complications	0	1 (2.9%)	1 (1.3%)	2 (2.5%)	0	2 (2.7%)	2 (1.3%)
Clavicle Fracture*	0	1 (2.9%)	1 (1.3%)	0	0	1 (1.3%)	1 (0.7%)
Postoperative Ileus	0	0	0	0	0	1 (1.3%)	1 (0.7%)
Rib Fracture*	0	1 (2.9%)	1 (1.3%)	0	0	1 (1.3%)	1 (0.7%)
Scapula Fracture*	0	1 (2.9%)	1 (1.3%)	0	0	1 (1.3%)	1 (0.7%)
Animal Bite	0	0	0	1 (1.3%)	0	0	0
Skin Laceration	0	0	0	1 (1.3%)	0	0	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	0	1 (2.9%)	1 (1.3%)	2 (2.5%)	0	2 (2.7%)	2 (1.3%)
Carcinoid Tumour Pulmonary	0	0	0	0	0	1 (1.3%)	1 (0.7%)
Colon Adenoma	0	1 (2.9%)	1 (1.3%)	0	0	1 (1.3%)	1 (0.7%)
Prostate Cancer	0	0	0	1 (1.3%)	0	0	0
Rectal Cancer	0	0	0	1 (1.3%)	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	0	2 (5.7%)	2 (2.6%)	1 (1.3%)	0	2 (2.7%)	2 (1.3%)
Pneumomediastinum	0	1 (2.9%)	1 (1.3%)	0	0	1 (1.3%)	1 (0.7%)
Pneumothorax*	0	1 (2.9%)	1 (1.3%)	0	0	1 (1.3%)	1 (0.7%)
Asthma	0	0	0	1 (1.3%)	0	0	0
General Disorders and Administration Site Conditions	0	0	0	2 (2.5%)	1 (1.1%)	0	1 (0.7%)
Asthenia	0	0	0	0	1 (1.1%)	0	1 (0.7%)
Non-Cardiac Chest Pain	0	0	0	1 (1.3%)	0	0	0
Oedema Peripheral	0	0	0	1 (1.3%)	0	0	0
Cardiac Disorders	0	0	0	0	0	1 (1.3%)	1 (0.7%)
Atrial Fibrillation	0	0	0	0	0	1 (1.3%)	1 (0.7%)
Metabolism and Nutrition Disorders	0	1 (2.9%)	1 (1.3%)	0	0	1 (1.3%)	1 (0.7%)
Dehydration	0	1 (2.9%)	1 (1.3%)	0	0	1 (1.3%)	1 (0.7%)
Nervous System Disorders	0	0	0	2 (2.5%)	0	0	0
Ischaemic Stroke	0	0	0	1 (1.3%)	0	0	0
Status Migrainosus	0	0	0	1 (1.3%)	0	0	0
Vascular Disorders	0	1 (2.9%)	1 (1.3%)	0	0	1 (1.3%)	1 (0.7%)
Hypertensive Crisis	0	1 (2.9%)	1 (1.3%)	0	0	1 (1.3%)	1 (0.7%)
Immune System Disorders	0	0	0	1 (1.3%)	0	0	0
Anaphylactic Reaction	0	0	0	1 (1.3%)	0	0	0
Musculoskeletal and Connective Tissue Disorders	0	0	0	1 (1.3%)	0	0	0
Osteoarthritis	0	0	0	1 (1.3%)	0	0	0
Reproductive System and Breast Disorders	0	0	0	1 (1.3%)	0	0	0
Ovarian Mass	0	0	0	1 (1.3%)	0	0	0

Abbreviations: MedDRA= Medical Dictionary for Drug Regulatory Affairs; TEAEs=treatment-emergent adverse events
Note: Some patients may be represented in multiple columns if they changed treatment or dose level when entering the extension. Each column reflects number of unique patients. Events are counted within the treatment group at the start of the event.
Note: Adverse event terms were mapped according to MedDRA v21.1.
* These events were experienced by the same patient and occurred at the same time.
Source: ISS Table 8.3.1; ISS Table 8.3.2; ISS Listing 16.1.9

Table 35. Incidence of Treatment-Emergent Serious Adverse Events by System Organ Class: On Study Drug (BEACON study, Safety Population)

MedDRA System Organ Class[a]	Placebo N=1093 n (%)	Bardoxolone Methyl N=1092 n (%)
Patients with any Serious Adverse Event	**295 (27)**	**363 (33)**
Number of Serious Adverse Events	**557**	**717**
Cardiac disorders	84 (8)	124 (11)
Infections and infestations	63 (6)	79 (7)
Renal and urinary disorders	71 (6)	52 (5)
Metabolism and nutrition disorders	42 (4)	51 (5)
Gastrointestinal disorders	39 (4)	46 (4)
Respiratory, thoracic and mediastinal disorders	32 (3)	43 (4)
Nervous system disorders	35 (3)	37 (3)
General disorders and administration site conditions	20 (2)	29 (3)
Vascular disorders	18 (2)	20 (2)
Injury, poisoning and procedural complications	17 (2)	19 (2)
Musculoskeletal and connective tissue disorders	13 (1)	21 (2)
Blood and lymphatic system disorders	11 (1)	20 (2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (1)	11 (1)
Hepatobiliary disorders	8 (1)	4 (<1)
Psychiatric disorders	3 (<1)	3 (<1)
Eye disorders	2 (<1)	3 (<1)
Investigations	2 (<1)	3 (<1)
Reproductive system and breast disorders	3 (<1)	2 (<1)
Skin and subcutaneous tissue disorders	1 (<1)	4 (<1)
Ear and labyrinth disorders	1 (<1)	3 (<1)
Endocrine disorders	1 (<1)	1 (<1)
Immune system disorders	0	2 (<1)
Surgical and medical procedures	0	2 (<1)

Column header counts and denominators are the number of patients in the safety population. This table only includes serious adverse events with onset no more than 30 days after a patient's last dose of study drug.
[a] Each patient is counted at most once in each System Organ Class.
Source: Table 12.3.1.2.1-1

The overall frequency of SAEs in the pivotal study was lower in the combined bardoxolone group than placebo (10.4% vs. 18.8%). No clear pattern could be distinguished among the PTs, given the low numbers. The two most common serious TEAEs in both treatment arms were ESRD (2.6% bardoxolone vs. 2.5% placebo) and pneumonia (0% bardoxolone vs. 2.5% placebo). There is an evident dose dependency observed. Namely, 3.4% in 20mg and 17.3% patients in 30 mg bardoxolone group had a SAE in Alport syndrome analysis set. However, the clinical relevance is uncertain given the few cases and that the frequency was lower in the placebo group. In addition, the differences in baseline UACR in the dose groups may have had an impact on adverse events.

No bardoxolone methyl-treated paediatric patients experienced an SAE.

In the previous BEACON trial on patients with T2D and stage 4 CKD, the overall frequency of SAEs was increased in the bardoxolone arm compared to placebo (33% vs. 27%), mainly driven by a difference in the SOC cardiac disorders (11% vs. 8%). In this SOC, the most frequent PT was cardiac failure (4.8% vs. 3.7%). There was also a slight imbalance in infections and infestations (7.2% vs. 5.8%), mainly in the PT pneumonia (2.7% vs. 1.1%). There were 11 (1%) SAEs of fluid overload in the bardoxolone group, whereas no cases were reported in the placebo group. Few cases of oedema peripheral occurred, and the frequency was similar in the bardoxolone and placebo groups (4 cases [3.7%] vs. 5 cases [4.6%], respectively). For anaemia, 17 SAEs (1.6%) occurred in the bardoxolone group compared to 7 cases (0.6%) in the placebo group.

No deaths were reported in the Alport syndrome clinical trials in any treatment group (Analysis set A and B). Nevertheless, as noted in the "Guideline on the clinical investigation of medicinal products to prevent development/slow progression of chronic renal insufficiency", the composite of all-cause mortality and renal failure should always be reported. The applicant is asked to provide this.

The total clinical study program on bardoxolone encompassed studies of varying design and number of participants where the product was studied in different populations. From these studies (Analysis set D), 60 fatal cases (2.8%) occurred in bardoxolone treated patients and 31 cases (2.3%) in patients treated with placebo.

Most of the fatal cases are from the relatively large BEACON RCT where 44 (3.6%) deaths occurred in the bardoxolone group and 31 (2.5%) cases in the placebo group. Most cases were in the cardiovascular SOC (2.7% bardoxolone vs. 1.8% placebo) and an imbalance was observed for fatal heart failure (0.46% bardoxolone vs. 0.09% placebo) although the cases were few.

In summary, an imbalance in all-cause death has been observed in a large earlier study on (non-Alport syndrome patients) with stage 4 CKD and T2DM. In the entire safety data set, there is a small numerical imbalance in all-cause mortality that favours placebo, however the varying types of studies included in the dataset limits the interpretation. Importantly, in the studies on Alport disease, no cases of death have been reported. However, the underlying cardiovascular risk is lower in these studies than the previous study on stage 4 CKD and T2D, thus, as the patients get older and the cardiovascular risk likely increase (given that bardoxolone is intended as a lifelong treatment), the long-term effect on mortality is an uncertainty.

Cardiovascular safety is a topic of special interest for the proposed indication and further discussed below.

3.3.7.4. Adverse events of special interest

End Stage Renal Disease (ESRD)

In Alport syndrome data pool, there were 6 cases of ESRD in bardoxolone treated patients, but one event occurred more than 2 months after study drug discontinuation. The other 5 patients (3.3% in Alport sy analysis set) had initially low indicators of renal function (CKD stage 3 and 4, and A3 stage of albuminuria [UACR ≥300 mg/g]), all received 30mg dose of bardoxolone, and were discontinued from the therapy. In the phase 3 study, a similar number of TEAEs of ESRD was reported in both treatment arms (2 cases in each arm). The other 3 cases of TEAE ESRD in bardoxolone treated patients occurred in the phase 2 study. In the entire study set B, the frequency of the TEAE ESRD was 3.3% (5) and 2.5% (2), respectively, in bardoxolone and placebo treated subjects (see also Exploratory Efficacy Analysis: Kidney Failure Composite Outcome under the efficacy section).

Cardiovascular Safety

The previous BEACON study with bardoxolone in patients with T2D and stage 4 CKD was terminated early due to increase in heart failure events (HR=1.83). The cases occurred within the first weeks of treatment and was possibly due to fluid retention. Elevated baseline BNP and prior hospitalization for heart failure was identified as risk factors, increasing the risk of heart failure by 60%.

In the BEACON study, there was an overall imbalance in SAEs (30.3% bardoxolone vs. 25.2% placebo) which was more pronounced in the SOC Cardiac disorders (10.0% vs. 6.8%). When the data was analysed for risk factors for fluid overload, the overall frequency of SAEs in patients without these risk factors was similar in the two treatment groups (21.0% bardoxolone vs. 19.7% placebo), however in the SOC cardiac disorders there was still a small imbalance (5.1% [40] vs. 3.8% [31]). No clear pattern among the PTs could be distinguished given the few cases.

As a safety measure, Alport patients with uncontrolled diabetes, elevated BNP levels and history of cardiac disease (e.g., cardiac insufficiency NYHA III-IV, LVEF <40%, previous hospitalization for heart failure, symptomatic coronary disease) were excluded in study 1603 and 1803, respectively.

It is acknowledged that patients with Alport syndrome generally do not have the severe comorbidities and cardiovascular risks associated with T2DM and Stage 4 CKD. However, if bardoxolone is considered as a lifelong treatment, the risk factors in the population will likely increase over time; therefore, this particular risk cannot be ruled out in the Alport population.

The applicant mentions that the more advanced kidney dysfunction in the previous BEACON study may have been one of the factors that contributed to the adverse outcome in the bardoxolone group. It is understood that patients with CKD stage 4-5 were excluded from the Alport studies as a part of the risk mitigation. With this background, it is noted that the proposed wording of the indication in the present SmPC includes subjects with ERSD. The applicant is therefore requested to justify the use of bardoxolone from a safety perspective in subjects with severe renal disease corresponding to CKD 4-5 or to reflect the limitations of the study population in the wording of the indication.

The applicant presented and discussed relevant CV safety issues but is somewhat diminishing a CV risk concluding that bardoxolone did not present an increased CV risk in Alport syndrome patients. AEs compatible with CV risk have been observed, and 30% of patients had AEs in SMQ Cardiac failure. Observed cardiac and vascular AEs of interest are BNP increased and oedema peripheral.

Bardoxolone increases BNP levels and likely promotes fluid retention and increases blood pressure with more advanced renal dysfunction (Chin, 2014b). Congestive heart failure (CHF) secondary to fluid overload has been included in the safety specification of proposed RMP as an important identified risk, which is agreed.

Brain Natriuretic Peptide

In the pivotal study (1602/phase 3), increases in mean BNP were observed with bardoxolone methyl treatment relative to baseline through 48 and 100 weeks of treatment. Values trended back to baseline at the Year 1 and Year 2 withdrawal periods, 4 weeks after stopping drug. Mean values remained below the upper limit of normal (<100 pg/L) throughout the study.

Values higher than 200 pg/mL were however observed in 10 individual patients in the treatment group; two of these displayed high values up to 544 pg/mL and 988 pg/mL, respectively. No such cases were observed in the placebo group.

In line with this finding and as discussed above, the PT Brain natriuretic peptide increased was reported in higher frequency of the subject treated with bardoxolone methyl (13.0%) compared to

placebo (3.8%) in the pivotal study. In addition, increases in NT-proBNP were reported in a few more cases in the bardoxolone than the placebo group (5.2% vs. 1%).

Consequently, even though the average increases in BNP by bardoxolone are mild, the substance appears to cause more pronounced increases in certain individuals. Given that elevated basal BNP levels were identified as a risk factor for development of Congestive heart failure (CHF) in previous studies with bardoxolone and considering that bardoxolone is intended for potential lifelong treatment, it is critical to define a safe target population, taking into account that cardiovascular (CV) risk factors increase over time. In addition, the applicant is requested to investigate whether elevated BNP levels were related to AEs within the cardiac disorders SOC, vascular disorders SOC and cardiac failure SMQ.

Blood pressure and ECG

Blood pressure was assessed throughout the pivotal trial and was not affected by the bardoxolone treatment. Of note, a slight increase in blood pressure was however observed in the previous BEACON study when assessed with ambulatory blood pressure monitoring 4 weeks after treatment initiation. Bardoxolone methyl patients had an increase in SBP (mean ± SD) at Week 4 (5.2 ± 10.5 mmHg) compared with a decrease in placebo patients (-2.8 ± 13.5 mmHg). For DBP, bardoxolone methyl patients had an increase (mean ± SD) at Week 4 of (2.7 ± 6.0 mmHg) compared with a decrease in placebo patients (-0.6-±-5.6 mmHg). Bardoxolone methyl patients had an increase in heart rate (mean ± SD) at Week 4 (4.0 ± 7.2 bpm) compared with a decrease in placebo patients (-0.1 ± 4.5 bpm). In the Alport studies, blood pressure was only assessed with cuff measurements and ambulatory blood pressure monitoring was not used. Provided that even small elevations in blood pressure may increase the CV risk if sustained over time, the applicant is requested to discuss the relevance of this finding in relation to the present Alport population.

Overall, very few cardiac arrhythmia related TEAS were reported in the studies performed in the proposed indication with no imbalance compared to placebo. ECGs were assessed throughout the pivotal study and no changes in the QT interval or other ECG parameters were observed.

Adverse Events Related to Cardiac Safety

TEAEs related to cardiovascular safety per SOC and SMQs from the pivotal study and analysis set B are presented in Table 36.

Table 36. Summary of Cardiovascular Treatment-Emergent Adverse Events (Analysis Set A and Analysis Set B)

	Analysis Set A		Analysis Set B
SOC/SMQ Preferred Term	**Bardoxolone Methyl N = 77**	**Placebo N = 80**	**Bardoxolone Methyl N = 153**
Cardiac disorders SOC	4 (5.2%)	6 (7.5%)	10 (6.5%)
Palpitations	2 (2.6%)	3 (3.8%)	3 (2.0%)
Angina pectoris	0	1 (1.3%)	1 (0.7%)
Bradycardia	0	1 (1.3%)	1 (0.7%)
Tachycardia	1 (1.3%)	1 (1.3%)	1 (0.7%)
Atrial Fibrillation	0	0	1 (0.7%)
Bundle Branch Block	0	0	1 (0.7%)
Cardiovascular insufficiency	1 (1.3%)	0	1 (0.7%)
Left Ventricular Hypertrophy	0	0	1 (0.7%)
Mitral Valve Incompetence	0	0	1 (0.7%)
Sinus arrhythmia	0	0	1 (0.7%)
Sinus Tachycardia	0	0	1 (0.7%)
Ventricular Extrasystoles	0	0	1 (0.7%)
Vascular disorders SOC	11 (14.3%)	13 (16.3%)	20 (13.1%)
Hypertension	8 (10.4%)	8 (10.0%)	14 (9.2%)
Hypotension	0	2 (2.5%)	3 (2.0%)
Hot flush	1 (1.3%)	1 (1.3%)	1 (0.7%)
Hypertensive crisis	1 (1.3%)	0	1 (0.7%)
Orthostatic hypotension	1 (1.3%)	0	1 (0.7%)
Varicose vein	1 (1.3%)	0	1 (0.7%)
Aortic dilatation	0	1 (1.3%)	0
Flushing	0	1 (1.3%)	0
Myocardial infarction SMQ	5 (6.5%)	8 (10.0%)	9 (5.9%)
Blood creatine phosphokinase increased	5 (6.5%)	8 (10.0%)	9 (5.9%)
Cardiac failure SMQ	21 (27.3%)	17 (21.3%)	46 (30.1%)
Oedema peripheral	12 (15.6%)	10 (12.5%)	22 (14.4%)
Brain natriuretic peptide increased	10 (13.0%)	3 (3.8%)	19 (12.4%)
N-terminal prohormone brain natriuretic peptide increased	4 (5.2%)	1 (1.3%)	15 (9.8%)
Prohormone brain natriuretic peptide increased	2 (2.6%)	0	5 (3.3%)
Peripheral swelling	2 (2.6%)	3 (3.8%)	4 (2.6%)

	Analysis Set A		Analysis Set B
SOC/SMQ Preferred Term	**Bardoxolone Methyl N = 77**	**Placebo N = 80**	**Bardoxolone Methyl N = 153**
Brain natriuretic peptide abnormal	0	1 (1.3%)	0
Ischaemic heart disease SMQ	6 (7.8%)	9 (11.3%)	11 (7.2%)
Blood creatine phosphokinase increased	5 (6.5%)	8 (10.0%)	9 (5.9%)
Angina pectoris	0	1 (1.3%)	1 (0.7%)
Electrocardiogram T wave inversion	1 (1.3%)	0	1 (0.7%)
Cardiomyopathy SMQ	6 (7.8%)	5 (6.3%)	11 (7.2%)
Palpitations	2 (2.6%)	3 (3.8%)	3 (2.0%)
Syncope	1 (1.3%)	1 (1.3%)	3 (2.0%)
Dyspnoea	2 (2.6%)	1 (1.3%)	2 (1.3%)
Chest pain	0	0	1 (0.7%)
Nocturia	0	0	1 (0.7%)
Orthostatic hypotension	1 (1.3%)	0	1 (0.7%)
Cardiac arrhythmias SMQ	4 (5.2%)	7 (8.8%)	9 (5.9%)
Palpitations	2 (2.6%)	3 (3.8%)	3 (2.0%)
Syncope	1 (1.3%)	1 (1.3%)	3 (2.0%)
Bradycardia	0	1 (1.3%)	1 (0.7%)
Tachycardia	1 (1.3%)	1 (1.3%)	1 (0.7%)
Atrial fibrillation		0	1 (0.7%)
Bundle branch block		0	1 (0.7%)
Sinus arrhythmia	0	0	1 (0.7%)
Sinus tachycardia		0	1 (0.7%)
Ventricular extrasystoles		0	1 (0.7%)
Heart rate irregular	0	1 (1.3%)	0
Arrhythmia related investigations, signs and symptoms SMQ	4 (5.2%)	6 (7.5%)	7 (4.6%)
Palpitations	2 (2.6%)	3 (3.8%)	3 (2.0%)
Syncope	1 (1.3%)	1 (1.3%)	3 (2.0%)
Bradycardia	0	1 (1.3%)	1 (0.7%)
Tachycardia	1 (1.3%)	1 (1.3%)	1 (0.7%)
Shock-associated circulatory or cardiac conditions (excl torsade de pointes) SMQ	3 (3.9%)	0	4 (2.6%)
Acute kidney injury	2 (2.6%)	0	3 (2.0%)
Cardiovascular insufficiency	1 (1.3%)	0	1 (0.7%)
Torsades de pointes, shock-associated conditions SMQ	2 (2.6%)	0	3 (2.0%)
Acute kidney injury	2 (2.6%)	0	3 (2.0%)
Other ischaemic heart disease SMQ	1 (1.3%)	1 (1.3%)	2 (1.3%)
Angina pectoris	0	1 (1.3%)	1 (0.7%)
Electrocardiogram T wave inversion	1 (1.3%)	0	1 (0.7%)
Torsades de pointes/QT prolongation SMQ	1 (1.3%)	1 (1.3%)	3 (2.0%)
Syncope	1 (1.3%)	1 (1.3%)	3 (2.0%)
Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) SMQ	0	1 (1.3%)	4 (2.6%)
Atrial fibrillation	0	0	1 (0.7%)
Bundle branch block	0	0	1 (0.7%)
Sinus arrhythmia	0	0	1 (0.7%)
Sinus tachycardia	0	0	1 (0.7%)
Ventricular extrasystoles	0	0	1 (0.7%)
Heart rate irregular	0	1 (1.3%)	0
Central nervous system vascular disorders SMQ	0	1 (1.3%)	0
Ischaemic stroke	0	1 (1.3%)	0
Embolic and thrombotic events SMQ	0	1 (1.3%)	0
Ischaemic stroke	0	1 (1.3%)	0
Embolic and thrombotic events, arterial SMQ	0	1 (1.3%)	0
Ischaemic stroke	0	1 (1.3%)	0

Abbreviations: MedDRA= Medical Dictionary for Drug Regulatory Affairs; SMQ=Standardized MedDRA Query; SOC=System Organ Class
Source: ISS Table 8.1.1; ISS Table 8.1.2; ISS Table 13.1.1; ISS Table 13.1.2

In Analysis Set A, the number of patients reporting TEAEs in the Cardiac disorders SOC or Vascular disorders SOC was slightly lower in the bardoxolone methyl group compared to the placebo group. No clear pattern could be distinguished among the PTs.

Within the cardiac failure SMQ, oedema peripheral was the most common PT, and the overall frequency was slightly higher in bardoxolone than in placebo treated subjects (15.6% vs. 12.5%).

One severe case and 6 (3.9%) cases of moderate peripheral oedema were reported in bardoxolone treated subjects while 0 moderate and 1 severe case were reported for placebo treated subjects. Most of them resolved with bardoxolone interruption and/or diuretic treatment while some resolved spontaneously without change of treatment. The frequency of mild cases was similar in bardoxolone and placebo treated subjects (9.8% vs. 11.3%). Thus, the frequency of peripheral oedema was slightly higher in the bardoxolone group, and there were more cases of moderate severity. In addition, there were cases of peripheral swelling reported (bardoxolone: 2 mild, 2 moderate; placebo: 3 mild).

Small decreases in haemoglobin, haematocrit, erythrocytes were observed in the bardoxolone group (see Laboratory findings) which may reflect an increased plasma volume.

As previously discussed, the BEACON study with bardoxolone was terminated early due to an increase in heart failure events associated with fluid retention in the treatment group. In the present Alport population with lower cardiovascular risk, no cases of heart failure occurred, but cases of increased BNP levels and peripheral oedema were more frequent in the bardoxolone group. Considering that bardoxolone is intended for potential lifelong treatment, it is critical to define a safe target population, taking into account that cardiovascular risk factors increase over time. Additional justification is requested. Subjects with NYHA III-IV were excluded from the pivotal study to reduce the potential for fluid overload and it is assumed that no patients with NYHA II were included in the study; however, the applicant proposes a contraindication for subjects with NYHA IV only. The applicant should justify the safe use of bardoxolone in subjects with symptomatic heart failure or include these subjects in the contraindication. Considering the increased risk of fluid retention and also the observation of increased BNP in the study in Alport subjects, and that bardoxolone is intended for potential lifelong treatment, it should be discussed how other cardiovascular risk factors should be monitored and handled during treatment. The applicant should also discuss if additional contraindications/precautions should be applied.

Although an absence of overt heart failure, signs of fluid overload (peripheral oedema and rise in BNP) occurred with common frequency, and in a population of young patients (below 40 years in median), strictly selected to minimise the risk, and over a short-term course of treatment. The applicant is requested to analyse data for risk factors (e.g., baseline CKD stage, use of ACE-Is/ARBs) predisposing to peripheral oedema and rise in BNP, as this would serve to pose contraindications and to develop better patient management and, eventually, limiting the indication. Moreover, it is unclear what the management of treatment would be in the event that patients develop such signs (interruption, discontinuation?). Recommendations should be reflected in the SmPC.

In addition, the applicant is requested to present narratives from the additional cases of peripheral swelling in Alport patients and also present data on BNP/NT-proBNP levels for all cases of peripheral oedema/peripheral swelling.

Hepatic Safety

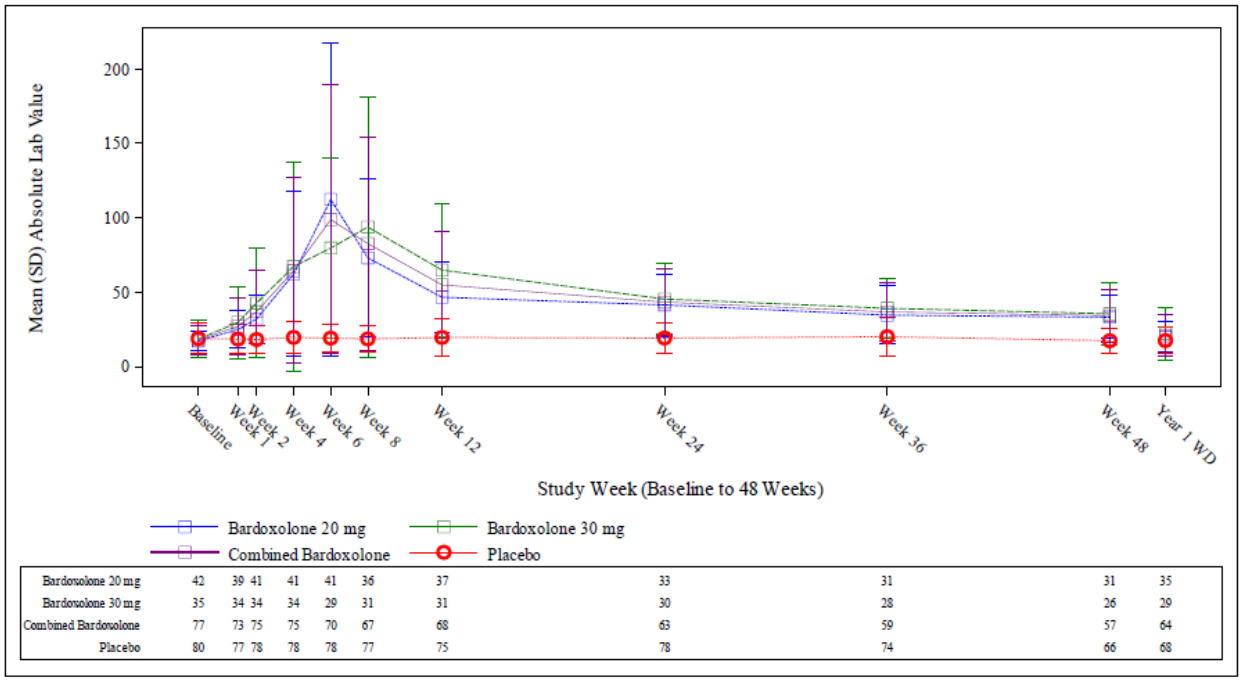
Hepatic safety was assessed as a safety topic of interest given observations of transient elevations in serum aminotransferases (ALT and AST) and GGT in previous clinical studies with bardoxolone. The clinical studies in Alport patients included criteria for discontinuing treatment in patients with ALT/AST elevations above certain levels that depended on accompanying bilirubin levels and clinical symptoms.

- *Alkaline Phosphatase*

A small but distinct change in ALP was observed in bardoxolone treated subjects compared to placebo. The changed appeared to be most pronounced at week 48. In analysis set A, the change from baseline was 5.6 U/L in the combined bardoxolone treated patients vs. -2.3 U/L in the placebo group. In analysis set B, the change from baseline was 8.6 U/L in the combined bardoxolone treated patients.

- *Alanine Aminotransferase*
- Mean absolute ALT in Analysis Set A is shown in Figure 15 (baseline to Week 48).

Figure 15: Mean Absolute ALT Levels (U/L), Baseline to Week 48 (Analysis Set A)



Abbreviations: Lab=laboratory; SD=standard deviation; WD=withdrawal
Source: ISS Figure 4.1.1

Figure 16: Mean Absolute ALT Levels (U/L), Baseline to Week 48 (Analysis Set A)

Patients treated with bardoxolone exhibited increased levels of ALT that peaked at Week 6 (20 mg) or Week 8 (30 mg) whereupon levels decreased but stayed elevated throughout the study. After the 1- and 2-year withdrawal visits, ALT levels decreased to below the Upper Limit of Normal (ULN) in most patients.

Correspondingly, in the pivotal study, 90% of the bardoxolone methyl-treated patients had increases in ALT above the ULN any time during the study compared to 21% in the placebo group. (Table 37).

Table 37. Treatment-Emergent Abnormal ALT (Analysis Set A and Analysis Set B)

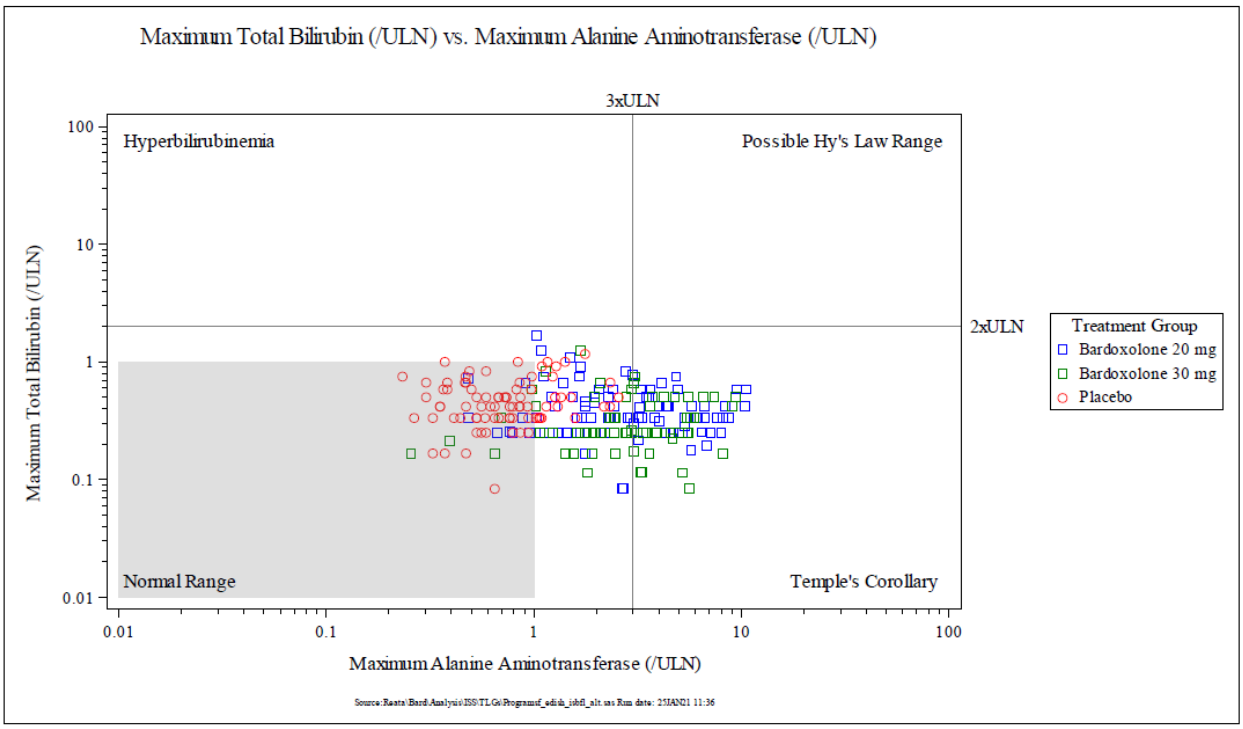
		Analysis Set A		Analysis Set B
Laboratory Parameter	**Abnormality Category**	**Bardoxolone Methyl N (%)**	**Placebo N (%)**	**Bardoxolone Methyl N (%)**
ALT (mg/dL)	Patients with Normal Baseline and at Least One On-treatment Value	75	77	146
	One or More On-treatment Low	0	1 (1.3%)	1 (0.7%)
	One or More On-treatment High	68 (90.7%)	16 (20.8%)	133 (91.1%)

Abbreviations: ALT=alanine aminotransferase
Source: ISS Table 16.2.1; ISS Table 16.2.2

Two bardoxolone methyl-treated patients in analysis set B had ALT values ≥10× ULN. The applicant is asked to clearly indicate the frequencies of subjects with ALT levels > 3 ULN, >5 ULN and 10 ULN respectively in the pivotal study.

In the pivotal study, 7.8% bardoxolone and 0% placebo treated patients withdrew due to ALT increased.

Increases in ALT were not associated with increases in total bilirubin. As shown in Figure 16, none of the patients randomized to bardoxolone methyl had maximum ALT or total bilirubin values that met potential Hy's law criteria (i.e., ALT ≥3× ULN and total bilirubin >2× ULN).

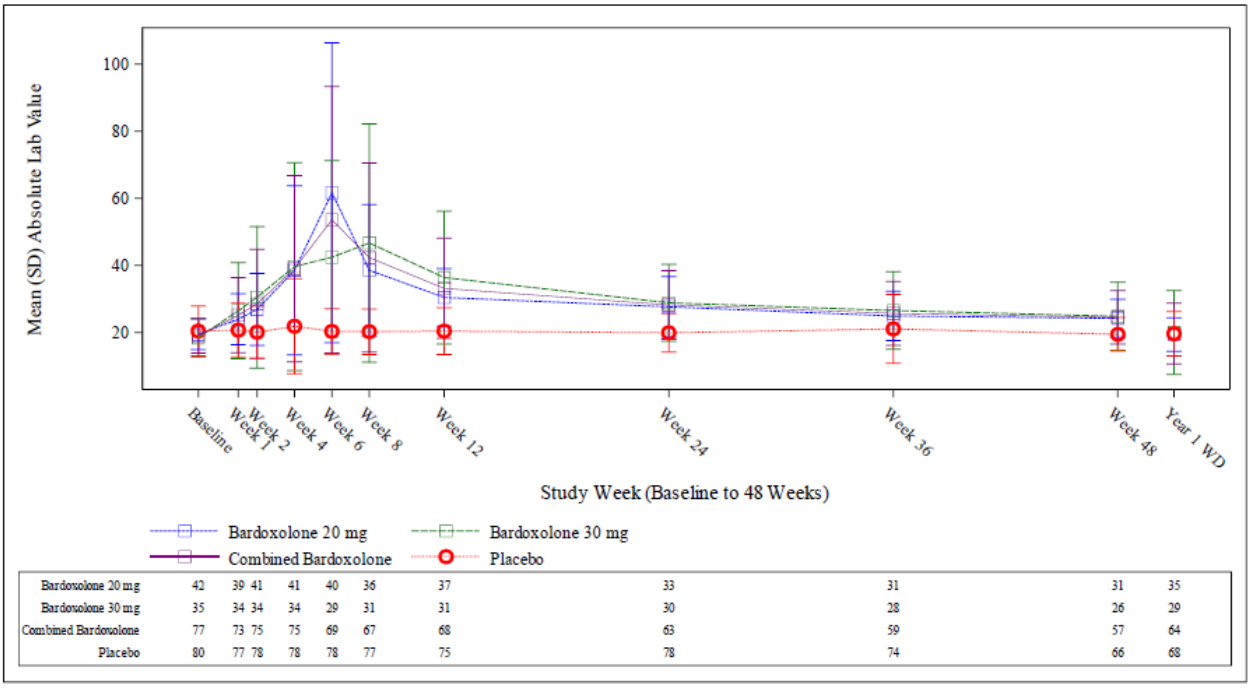


Abbreviation: ALT= alanine aminotransferase; ULN=upper limit of normal
Source: ISS Figure 1.1.2

Figure 17: Maximum Total Bilirubin vs Maximum ALT (Analysis Set B)

Aspartate Aminotransferase

Mean absolute AST are shown for Analysis Set A in Figure 17 (baseline to Week 48).



Abbreviations: AST=aspartate aminotransferase; Lab=laboratory; SD=standard deviation; WD=withdrawal
Source: ISS Figure 4.1.1

Figure 18: Mean Absolute AST Levels (U/L), Baseline to Week 48 (Analysis Set A)

Most bardoxolone treated patients displayed increased AST above ULN. Peak levels were observed at Week 6 (for patients receiving 20 mg) or Week 8 (for patients receiving 30 mg). After the 1- and 2-year withdrawal visits, AST levels decreased to below the ULN in most patients within 4 weeks.

Correspondingly, in the pivotal study, 82% of the subjects in the bardoxolone methyl-treated patients had increases in AST above the ULN any time during the study compared to 19% in the placebo group. The applicant is asked to clearly indicate the frequencies of subjects with AST levels > 3 ULN, >5 ULN and 10 ULN respectively in the pivotal study.

In the pivotal study, 3.9% bardoxolone and 0% placebo treated patients withdrew due to AST increased.

Association of ALT and AST with Adverse Events

For 6 bardoxolone treated patients, elevations in ALT or AST occurred within 14 days of the onset of TEAEs of nausea, anorexia, abdominal pain, or fatigue (Table 38). The elevations were not associated with cases of severe TEAEs, and, according to the applicant, not associated with symptoms consistent with liver injury.

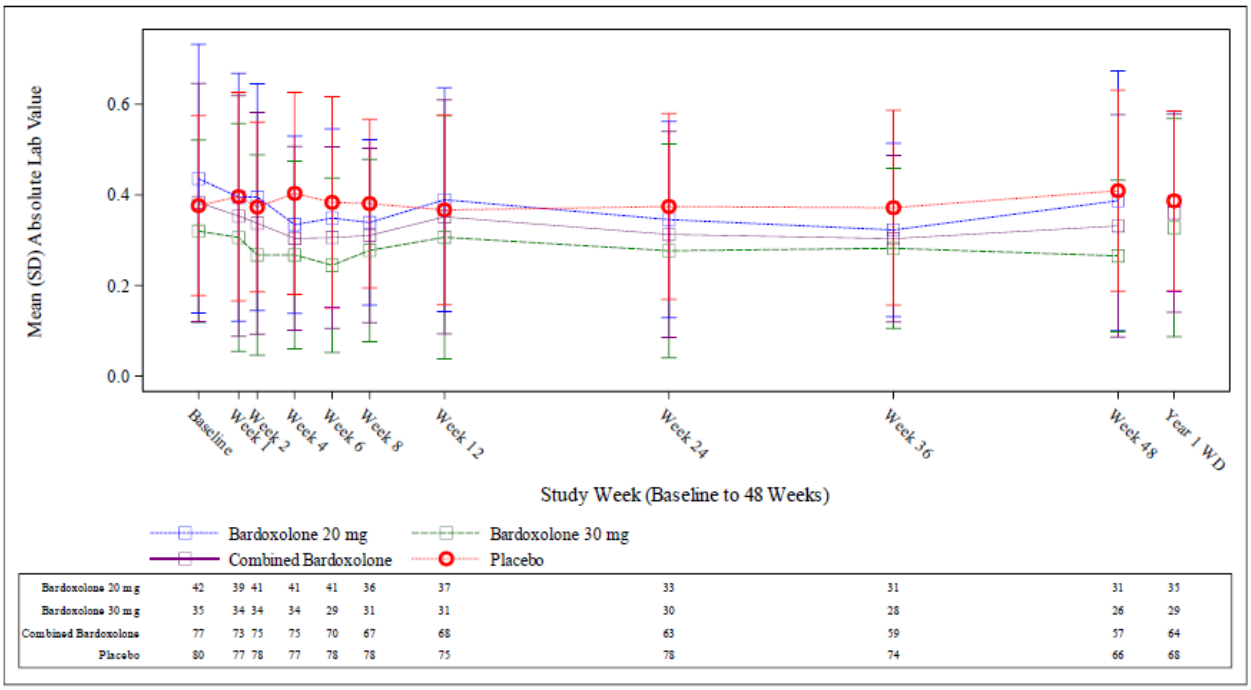
Table 38. Summary of Moderate or Severe Treatment-Emergent Adverse Events Occurring within 14 Days of ALT or AST Elevations (Analysis Set A and Analysis Set B).

	Analysis Set A		Analysis Set B
Criteria category	**Bardoxolone Methyl (N = 77)**	**Placebo (N = 80)**	**Bardoxolone Methyl (N = 153)**
Abnormality: Elevation of ALT or AST in temporal association with nausea, vomiting, anorexia, abdominal pain, or fatigue	6 (7.8%)	1 (1.3%)	6 (3.9%)
Abnormality: Elevation of ALT or AST in temporal association with abdominal pain	1 (1.3%)	0	1 (0.7%)
Abnormality: Elevation of ALT or AST in temporal association with fatigue	4 (5.2%)	1 (1.3%)	4 (2.6%)
Abnormality: Elevation of ALT or AST in temporal association with nausea	2 (2.6%)	0	2 (1.3%)
Abnormality: Elevation of ALT or AST in temporal association with vomiting	0	0	0

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase
Source: ISS Table 19.1.1; ISS Table 19.1.2

Total Bilirubin

Mean changes from baseline in total bilirubin for Analysis Set A are shown in Figure 18 (baseline to Week 48). Decreases in bilirubin below the ULN were observed in 50.8% of patients treated with bardoxolone in Analysis Set A compared to 36.1% in the placebo group (Table 39). Values were lowest between week 2-8 and stayed decreased throughout the treatment period and returned to baseline after treatment discontinuation.



Abbreviations: Lab=laboratory; SD=standard deviation; WD=withdrawal
Source: ISS Figure 4.1.1

Figure 19: Mean Absolute Total Bilirubin Levels (mg/dL), Baseline to Week 48 (Analysis Set A)

Table 39. Treatment-Emergent Abnormal Total Bilirubin (Analysis Set A and Analysis Set B)

		Analysis Set A		Analysis Set B
Laboratory Parameter	**Abnormality Category**	**Bardoxolone Methyl N (%)**	**Placebo N (%)**	**Bardoxolone Methyl N (%)**
Total Bilirubin (mg/dL)	Patients with Normal Baseline and at Least One On-treatment Value	65	72	126
	One or More On-treatment Low	33 (50.8%)	26 (36.1%)	44 (34.9%)
	One or More On-treatment High	2 (3.1%)	0	2 (1.6%)

Source: ISS Table 16.2.1; ISS Table 16.2.2

The applicant states "decreases below the ULN". The applicant is requested to clarify whether decreases occurred below the ULN as stated, or below the LLN. The reference values for LLN and ULN should also be provided.

Three (3.9%) bardoxolone treated patients with normal baseline values in the pivotal study displayed increased bilirubin values (>ULN) at some point during the treatment period, but none exceeded 2× ULN. Increases in bilirubin was not registered for placebo-treated patients with normal values at baseline. The applicant is requested to verify the number of patients with increased bilirubin values given that there appears to be a discrepancy between the numbers given in Table 39 in this overview and Table 43 in the submitted SCS. According to Table 39, 2 subjects displayed high bilirubin whereas there appears to be 3 subjects according to the Table 43 in the submitted SCS.

The reduction in bilirubin appears more pronounced in the paediatric population however the values were more scattered.

The applicant is requested to discuss the mechanism and clinical relevance for the general reduction in bilirubin observed after bardoxolone administration, also considering the more pronounced effect in the paediatric population.

Gamma-Glutamyl Transferase

Gamma-Glutamyl Transferase (GGT) increased above the ULN in 36.8% of bardoxolone-treated subjects. (Table 40) The maximal rise was observed in week 8 after treatment initiation.

Table 40. Treatment-Emergent Abnormal GGT (Analysis Set A and Analysis Set B).

		Analysis Set A		Analysis Set B
Laboratory Parameter	**Abnormality Category**	**Bardoxolone Methyl N (%)**	**Placebo N (%)**	**Bardoxolone Methyl N (%)**
GGT (U/L)	Patients with Normal Baseline and at Least One On-treatment Value	76	75	136
	One or More On-treatment Low	3 (3.9%)	2 (2.7%)	3 (2.2%)
	One or More On-treatment High	20 (26.3%)	4 (5.3%)	50 (36.8%)

Abbreviations: GGT=gamma-glutamyl transferase
Source: ISS Table 16.2.1; ISS Table 16.2.2

Adverse Events Related to Hepatic Safety

Table 41 summarizes the TEAEs related to hepatic safety. No SAEs related to hepatic safety were reported in any patient. The majority of the hepatic TEAEs related to hepatic safety occurred within the first 12 weeks of treatment. In Analysis Set B, 62 of the 65 patients with ALT increased had onset in the first 12 weeks; 31 of the 34 patients with AST increased had onset in the first 12 weeks, and 9 of the 10 patients with GGT increased had onset in the first 12 weeks.

Table 41. Summary of Hepatic Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Analysis Set A and Analysis Set B).

	Analysis Set A		Analysis Set B
System Organ Class **Preferred Term**	**Bardoxolone Methyl** **(N = 77)**	**Placebo** **(N = 80)**	**Bardoxolone Methyl** **(N = 153)**
Hepatobiliary disorders			
Hepatic function abnormal	3 (3.9%)	0	3 (2.0%)
Hepatic Steatosis	0	0	2 (1.3%)
Drug-Induced Liver Injury	0	0	1 (0.7%)
Steatohepatitis	1 (1.3%)	0	1 (0.7%)
Investigations			
Alanine aminotransferase increased	36 (46.8%)	1 (1.3%)	65 (42.5%)
Aspartate aminotransferase increased	19 (24.7%)	0	34 (22.2%)
Gamma-glutamyltransferase increased	4 (5.2%)	1 (1.3%)	10 (6.5%)

Source: ISS Table 8.1.1; ISS Table 8.1.2

In the pivotal study, 7.8% (6) and 3.9% (3) bardoxolone and 0% placebo treated patients withdrew due to ALT and AST increased, respectively. No additional patients withdrew in analysis set B. In total, five bardoxolone methyl-treated patients stopped treatment due to protocol-specified drug withdrawal criteria for ALT or AST elevations. The applicant should clarify whether these cases represent additional cases than those presented under discontinuations due to AEs.

In the entire analysis set B, 7 TEAEs within SOC Hepatobiliary disorders were registered in bardoxolone treated patients (no cases in placebo group). 3 cases concerned hepatic steatosis/steatohepatitis, 1 case concerned drug-induced liver injury and 3 cases concerned hepatic function abnormal. Short narratives have been provided but the full narratives are requested. Regarding the cases of steatohepatitis and drug induced liver injury, it is of relevance whether diagnosis was based entirely on increases in liver enzymes or whether there were clinical signs of liver injury.

Muscle Spasms

A summary of the muscle spasm TEAEs is provided in Table 42.

Table 42. Consolidated Summary of Muscle Spasms Treatment-emergent Adverse Events (Analysis Set A and Analysis Set B)

	Analysis Set A		Analysis Set B
	Bardoxolone Methyl (N = 77)	Placebo (N = 80)	Bardoxolone Methyl (N = 153)
N (%) of Patients	38 (49.4%)	28 (35.0%)	72 (47.1%)
N (%) of Patients <18 years	5 (45.5%)	4 (33.3%)	5 (25.0%)
N (%) of Patients 18 to ≤65 years	33 (50.0%)	22 (33.3%)	66 (50.4%)
N (%) of Patients 66 to ≤75 years	0	2 (100%)	1 (50.0%)
Short Term ≤4 weeks	15 (19.5%)	17 (21.3%)	24 (15.7%)
Short Term ≤12 weeks	26 (33.8%)	24 (30.0%)	49 (32.0%)
Long Term >12 to ≤24 weeks	11 (14.3%)	5 (6.3%)	17 (11.1%)
Long Term >24 to ≤52 weeks	9 (11.7%)	4 (5.0%)	20 (13.1%)
Long Term >52 weeks	6 (7.8%)	2 (2.5%)	22 (14.4%)
Related	33 (42.9%)	19 (23.8%)	61 (39.9%)
Severity:			
Mild	26 (33.8%)	18 (22.5%)	44 (28.8%)
Moderate	9 (11.7%)	9 (11.3%)	20 (13.1%)
Severe	3 (3.9%)	1 (1.3%)	8 (5.2%)
Study Drug Discontinuation	2 (2.6%)	0	2 (1.3%)
Study Drug Interruption	2 (2.6%)	1 (1.3%)	4 (2.6%)
Serious	0	0	0
Withdrawal Period	1 (1.3%)	2 (2.5%)	2 (1.3%)
Mean (SE) of Days to Event	294.3 (27.24)	427.2 (32.06)	467.8 (30.81)
Median Days to Event	311.0	NA	729.0

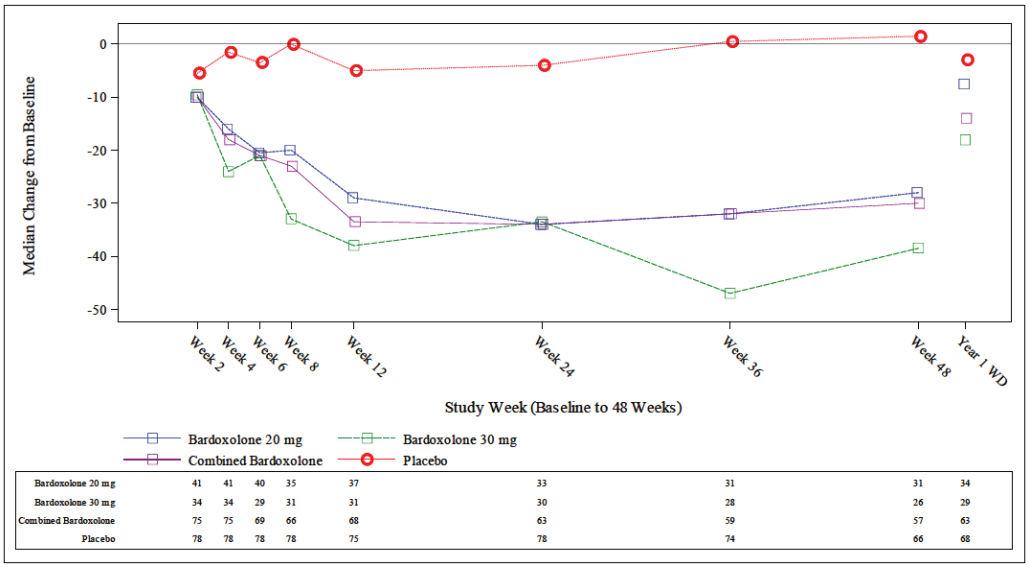
Abbreviations: NA=not applicable; SE=standard error
Sources: ISS Table 7.2; ISS Table 8.1.1.1.9; ISS Table 8.1.2.1.9; ISS Table 8.4.1; ISS Table 8.4.2; ISS Table 8.9.1; ISS Table 8.9.2

Muscle spasms were frequent in both treatment arm, but the frequency was higher in bardoxolone treated subjects compared to placebo. The imbalance was primarily seen in the long term, i.e. after more than 12 weeks of treatment. The cases were usually mild, although there were 2 cases of study drug discontinuations. Also, in the previous BEACON study in patients with stage 4 CKD and T2D, muscle spasm was more frequent in bardoxolone treated patients than placebo (42% vs. 15%). The frequency of severe muscle spasm was 5% vs. 1%. The risk for muscle spasm is reflected in SmPC section 4.8.

Provided that hypomagnesemia may be related to muscle spasms and that bardoxolone lowers serum magnesium levels, an analysis of magnesium levels in subjects reporting muscle spasm vs these without muscle spasm should be provided.

Creatine Kinase

Bardoxolone methyl treatment was associated with decreases in CK. Due to the non-normal distribution of creatine kinase values, median changes from baseline have also been plotted and are provided in Figure 19 (baseline to 48 weeks).



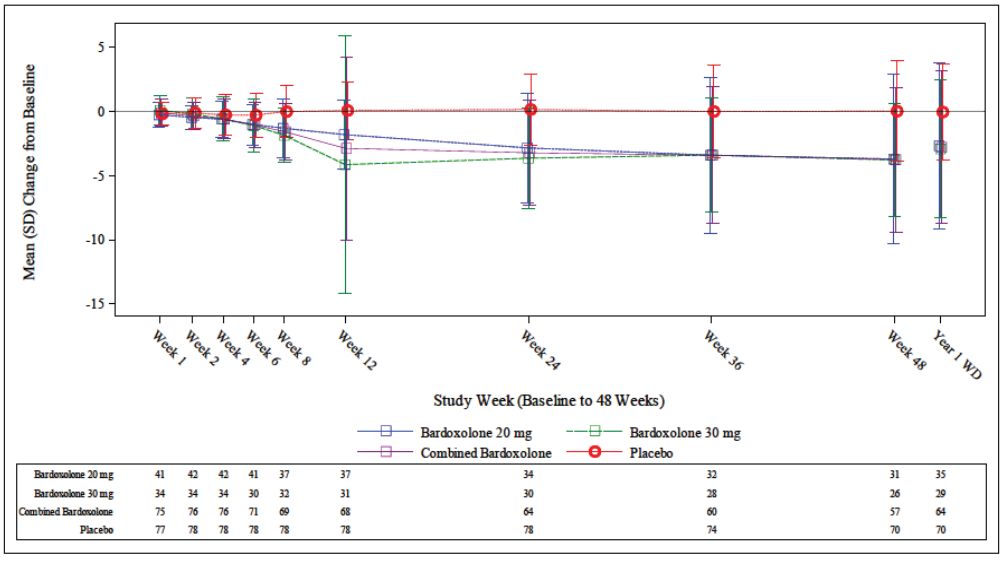
Abbreviation: WD=withdrawal
Source: ISS Figure 4.6.1

Figure 20: Median Changes in Creatine Kinase Levels (U/L), Baseline to Week 48 (Analysis Set A)

Bardoxolone treated subjects displayed decreased values of creatine kinase (CK) that were sustained throughout the study period. Patients experiencing muscle spasm had similar median decreases from baseline in CK to those seen in patients without muscle spasms. The findings are therefore not indicative of muscle damage as a cause for the spasms.

Weight Changes

Mean changes in weight from baseline are shown for Analysis Set A in Figure 20 (baseline to Week 48).



Abbreviations: SD=standard deviation; WD=withdrawal
Source: ISS Figure 3.2.1

Figure 21: Mean Change from Baseline in Weight (kg), Baseline to Week 48 (Analysis Set A)

Bardoxolone treated patients displayed a weight decrease that was most pronounced during the first 12 weeks. At week 100, the change was -3.35 vs. 0.16 kg for bardoxolone vs. placebo. Weight loss

was more pronounced in patients with high BMI (≥30 kg/m^2) at baseline. No data is available on patients with low BMI (<18.5 kg/m^2).

Weight decreases seem to be dependent on the baseline BMI. Patients with BMI ≥30 kg/m^2 experienced more weight loss over 48 weeks of treatment compared to those with BMI<30 kg/m^2. Mean decreases in weight were apparent by Week 6, continued through Week 12, and tended to plateau between Weeks 12 through Week 48. 7.8% of patients experienced significant weight loss of >7%.

There were 20 paediatric patients treated with bardoxolone in total. Five of these patients had BMI values drop below 18.5 kg/m^2, however, 3 of them gained weight during the study and BMI returned to baseline.

In the studies on Alport patients, there was an imbalance in TEAE diarrhoea (15.6% vs. 7.5%). From the entire analysis set C, an imbalance in nausea (18.2% vs. 14%) and vomiting (10.7% vs. 7.6%) is observed in relation to bardoxolone. The applicant is requested to discuss whether the TEAEs within SOC gastrointestinal disorders are related to the observed weight loss.

Infections and Infestations

PTs within the Infections and infestations SOC were assessed by the applicant as TEAEs of interest due to the hypothetical concern, that the anti-inflammatory effects associated with Nrf2 activation may lead to a decreased innate immune response.

TEAEs in the Infections and infestations SOC for are presented in Table 43.

Table 43. Summary of Infections and Infestations Treatment-Emergent Adverse Events System Organ Class and Preferred Term (Analysis Set A and Analysis Set B)

	Analysis Set A		Analysis Set B
System Organ Class Preferred Term	**Bardoxolone Methyl (N = 77)**	**Placebo (N = 80)**	**Bardoxolone Methyl (N = 153)**
Infections and infestations	**45 (58.4%)**	**45 (56.3%)**	**78 (51.0%)**
Nasopharyngitis	19 (24.7%)	25 (31.3%)	26 (17.0%)
Upper respiratory tract infection	11 (14.3%)	8 (10.0%)	24 (15.7%)
Influenza	6 (7.8%)	7 (8.8%)	9 (5.9%)
Bronchitis	3 (3.9%)	2 (2.5%)	10 (6.5%)
Urinary tract infection	3 (3.9%)	5 (6.3%)	8 (5.2%)
Sinusitis	4 (5.2%)	6 (7.5%)	6 (3.9%)
Pneumonia	2 (2.6%)	2 (2.5%)	4 (2.6%)
Gastroenteritis	1 (1.3%)	1 (1.3%)	4 (2.6%)
Cystitis	3 (3.9%)	1 (1.3%)	3 (2.0%)
Ear infection	2 (2.6%)	1 (1.3%)	3 (2.0%)
Herpes zoster	0	1 (1.3%)	3 (2.0%)
Pharyngitis	1 (1.3%)	3 (3.8%)	2 (1.3%)
Viral infection	1 (1.3%)	1 (1.3%)	3 (2.0%)
Conjunctivitis	1 (1.3%)	1 (1.3%)	2 (1.3%)
Oral herpes	2 (2.6%)	1 (1.3%)	2 (1.3%)
Rhinitis	1 (1.3%)	3 (3.8%)	1 (0.7%)
Viral upper respiratory tract infection	2 (2.6%)	1 (1.3%)	2 (1.3%)
Fungal infection	1 (1.3%)	0	2 (1.3%)
Tonsillitis	1 (1.3%)	1 (1.3%)	1 (0.7%)
Otitis media	1 (1.3%)	1 (1.3%)	1 (0.7%)
Atypical pneumonia	1 (1.3%)	0	1 (0.7%)
Bacterial vaginosis	1 (1.3%)	0	1 (0.7%)
Campylobacter gastroenteritis	1 (1.3%)	0	1 (0.7%)
Clostridium difficile infection	0	0	1 (0.7%)
Corona virus infection	0	0	1 (0.7%)
Eye infection	0	0	1 (0.7%)
Fungal skin infection	0	0	1 (0.7%)
Furuncle	1 (1.3%)	0	1 (0.7%)
Gangrene	0	0	1 (0.7%)
Gastroenteritis viral	0	2 (2.5%)	0
Gastrointestinal infection	1 (1.3%)	0	1 (0.7%)
Impetigo	1 (1.3%)	0	1 (0.7%)
Lower respiratory tract infection	0	2 (2.5%)	0
Lyme disease	0	0	1 (0.7%)
Otitis externa	0	2 (2.5%)	0
Peritonitis	0	0	1 (0.7%)
Pharyngitis streptococcal	0	0	1 (0.7%)
Pneumonia bacterial	0	0	1 (0.7%)
Pyelonephritis	0	0	1 (0.7%)
Skin candida	0	0	1 (0.7%)
Tooth abscess	0	0	1 (0.7%)
Tooth infection	1 (1.3%)	0	1 (0.7%)
Acarodermatitis	0	1 (1.3%)	0
Conjunctivitis viral	0	1 (1.3%)	0
Empyema	0	1 (1.3%)	0
Eye infection viral	0	1 (1.3%)	0
Gastrointestinal viral infection	0	1 (1.3%)	0
Herpes ophthalmic	0	1 (1.3%)	0
Respiratory tract infection	0	1 (1.3%)	0
Tinea manuum	0	1 (1.3%)	0
Tonsillitis bacterial	0	1 (1.3%)	0

Source: ISS Table 12.1.1; ISS Table 12.1.2

The proportion of patients with infections and infestations and the time to onset was similar in bardoxolone and placebo treated subjects and involved a large number of PTs. There was a numerical

imbalance in cases of upper respiratory tract infections between bardoxolone and placebo treated subjects in the pivotal study (14.3% vs. 10%) but it may be a chance finding given the few cases and that it is a common condition. A similar rate was observed in analysis set B (15.7%). There was also an imbalance in cases of cough (10.4% vs. 3.8% in the placebo group). In the previous BEACON study in patients with stage 4 CKD and T2D, an imbalance for the PT pneumonia was observed (Bardoxolone 5% [51/1092] Placebo 2% [25/1093]). No imbalance was observed in the Alport population, but the cases are few which makes the estimate uncertain. Pneumonia in relation to bardoxolone should be discussed given the imbalance in cough and upper respiratory tract infections in the Alport population.

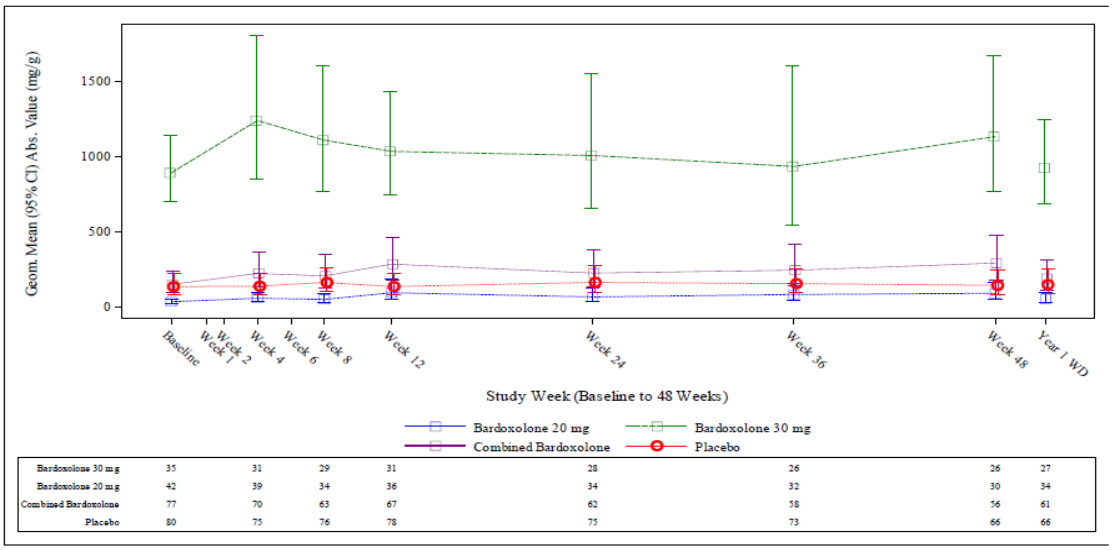
Magnesium

Hypomagnesaemia was identified as an AESI in formerly conducted studies. Serum magnesium levels were reduced by bardoxolone treatment compared to placebo. The reductions in serum magnesium were apparent within the first few weeks of treatment. Serum magnesium levels were lowest at Week 12 and were maintained low until week 48. The mean change at the last on-treatment visit was -0.06 ± 0.226 mEq/L for bardoxolone vs. 0.03 ± 0.155 mEq/L for placebo-treated patients in Analysis Set A. All patients had on-treatment serum magnesium levels ≥1.2 mEq/L throughout the trial.

Consequently, the changes in serum magnesium concentration were mild and no patients developed overt hypomagnesemia during the trial. It appears that it is not associated with QT interval prolongation. Possible mechanism is discussed by the applicant (intracellular shift of magnesium). Nevertheless, an analysis of this finding in relation to muscle spasms is requested (see previous 'Muscle spasm' section).

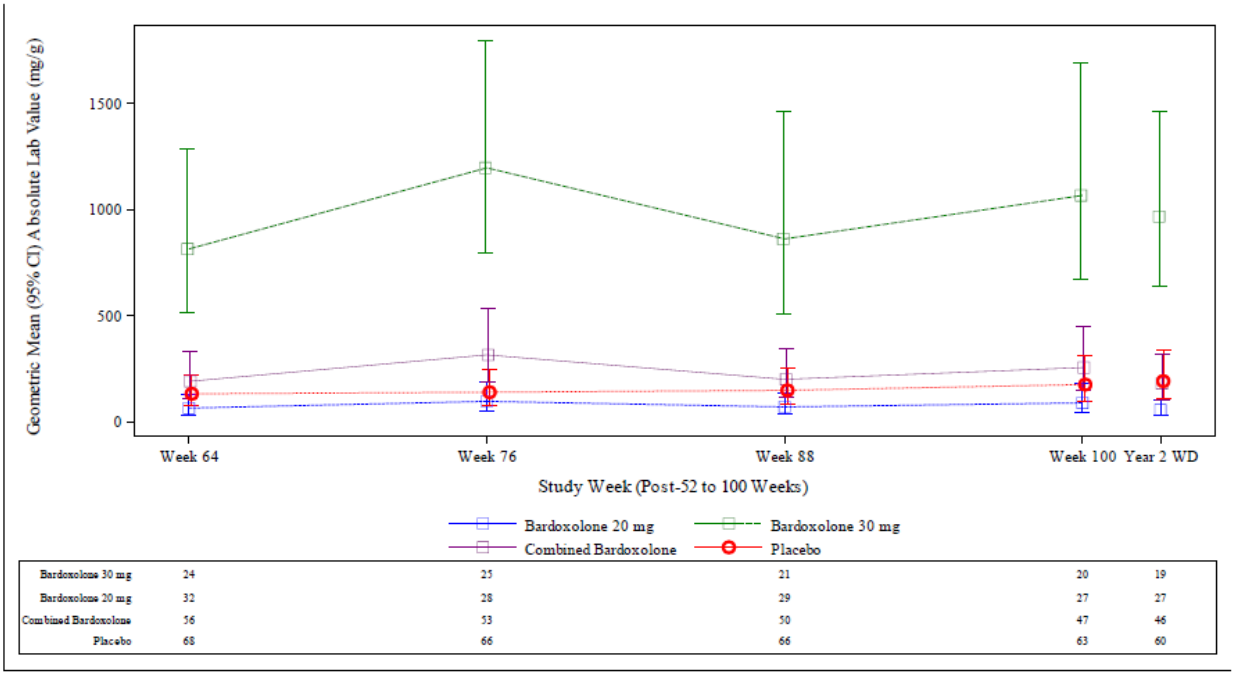
Changes in urine albumin creatinine ratio (UACR)

Geometric mean values in UACR in Analysis Set A are shown in Figure 21 (baseline to Week 48) and Figure 21 (Week 64 to Week 100).



Abbreviations: Abs=absolute; CI=confidence interval; Geom=geometric; UACR=urinary albumin-to-creatinine ratio; WD=withdrawal
Source ISS Figure 8.1.1

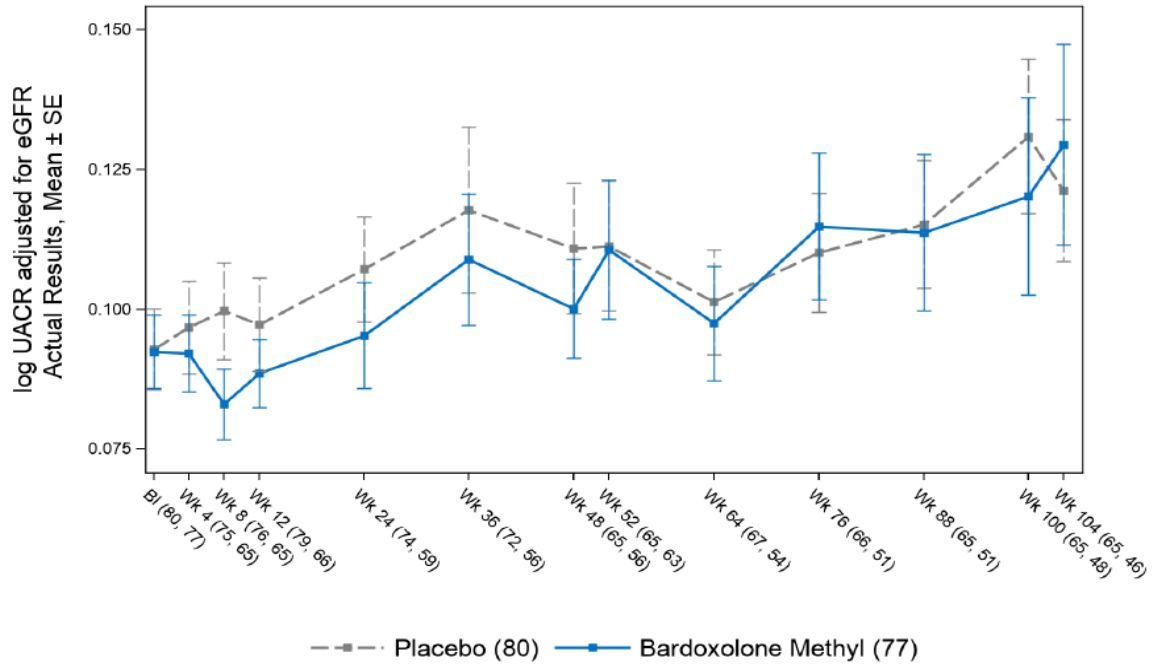
Figure 22: Geometric Mean UACR Values from Baseline (mg/g), Baseline to Week 48 (Analysis Set A)



Abbreviations: CI=confidence interval; Lab=laboratory; UACR=urinary albumin-to-creatinine ratio; WD=withdrawal
Source: ISS Figure 8.3.1

Figure 23: Geometric Mean UACR Values from Baseline (mg/g), Week 64 to Week 100 (Analysis Set A)

To provide a metric for expressing the excretion of albumin relative to GFR, log(UACR) values were normalized to eGFR to assess differences in the log(UACR)/eGFR ratio for patients by the randomized group for Analysis Set A (Figure 23).



Abbreviations: eGFR=estimated glomerular filtration rate; SEM=standard error of mean; UACR=urinary albumin-to-creatinine ratio
Note: Line plot arithmetic mean ± SEM natural log transformed UACR to eGFR over time in patients randomized to either placebo (gray line) or bardoxolone methyl (blue line). Periods between Weeks 48 and 52 and between Weeks 100 and 104 were off-treatment periods.
Source: Study 402-C-1603 Phase 3 CSR, Table 14.3.4.24.1

Figure 24: Log UACR/eGFR Ratio, Baseline to Week 104 (Analysis Set A)

An analysis of mean changes in eGFR by the Week 12 change from baseline UACR quartile (when increases in UACR were near maximal with bardoxolone methyl treatment) was performed for Analysis Set A.

Table 44 shows changes from baseline in eGFR at Weeks 48 and 100, and Table 45 shows off-treatment changes (4 weeks after last dose) in Year 1 and Year 2, for patients stratified by UACR changes at Week 12.

Table 44. On-treatment Changes from Baseline in eGFR by Quartiles of Week 12 UACR (Analysis Set A)

Treatment	Quartile	N	Geometric Mean UACR			Mean eGFR Change ± SD	
			Baseline	Week 12	Week 12 Change (UACR/Baseline UACR)	Week 48	Week 100
Bardoxolone Methyl	1	16	403.09	184.44	0.46	11.17 ± 13.528	4.96 ± 19.984
	2	17	136.87	156.50	1.14	9.29 ± 22.545	5.50 ± 19.711
	3	17	307.66	642.37	2.09	4.50 ± 9.510	-3.47 ± 12.988
	4	17	41.61	335.71	8.07	7.46 ± 8.624	5.66 ± 12.240
Placebo	1	19	198.58	66.86	0.34	-4.85 ± 8.325	-7.04 ± 10.701
	2	20	144.70	118.12	0.82	-4.85 ± 10.531	-11.78 ± 10.496
	3	19	163.00	221.38	1.36	-5.21 ± 7.898	-10.08 ± 10.301
	4	20	67.93	180.67	2.66	-3.46 ± 10.100	-6.62 ± 7.376

Abbreviations: eGFR=estimated glomerular filtration rate; SD=standard deviation; UACR=urinary albumin-to-creatinine ratio
Source: ISS Table 31.1.1

Table 45. Off-treatment Changes from Baseline in eGFR by Quartiles of Week 12 UACR (Analysis Set A)

Treatment	Quartile	N	Geometric Mean UACR			Mean eGFR Change ± SD	
			Baseline	Week 12	Week 12 Change (UACR/Baseline UACR)	Year 1 Withdrawal	Year 2 Withdrawal
Bardoxolone Methyl	1	16	403.09	184.44	0.46	3.00 ± 11.507	-5.44 ± 12.902
	2	17	136.87	156.50	1.14	0.41 ± 16.235	-2.75 ± 17.579
	3	17	307.66	642.37	2.09	-1.53 ± 13.023	-4.88 ± 14.705
	4	17	41.61	335.71	8.07	-0.94 ± 7.908	-3.28 ± 10.421
Placebo	1	19	198.58	66.86	0.34	-5.82 ± 7.612	-8.43 ± 12.193
	2	20	144.70	118.12	0.82	-5.34 ± 10.582	-9.66 ± 14.433
	3	19	163.00	221.38	1.36	-6.71 ± 7.945	-10.36 ± 9.108
	4	20	67.93	180.67	2.66	-3.14 ± 9.921	-4.62 ± 6.841

Abbreviations: eGFR=estimated glomerular filtration rate; SD=standard deviation; UACR=urinary albumin-to-creatinine ratio
Source: ISS Table 31.1.1

Per the Study 1603 protocol, patients with baseline UACR >300 mg/g were randomized to receive 30 mg of bardoxolone methyl while patients with baseline UACR ≤300 mg/g were randomized to receive 20 mg, which accounts for the higher UACR in the 30 mg dose group. Bardoxolone treated subjects displayed increased UACR from week 4 and onwards. UACR tended to decrease after treatment discontinuation.

When data was assessed based on UACR category, a slightly larger proportion of patients on bardoxolone shifted into a higher category than those on placebo (42.9% vs. 35%).

The applicant hypothesizes that the increase in UACR in bardoxolone treated patients is secondary to the increased GFR, due to increased delivery of albumin to the tubules. An analysis of log(UACR)/eGFR ratio for the treatment arms is presented. In this analysis, the ratio is similar at baseline in the two groups. Throughout the first year of treatment, the ratio is numerically lower in the bardoxolone arm

compared to placebo. However, during the second year of treatment, the curves seem to overlap, even though the ratio at week 100 is lower in the bardoxolone than the placebo group. Throughout the entire two-year period, the bardoxolone treated subjects demonstrate an increased ratio and the slope of the curve appears similar to that of the placebo group. Also, the apparent increased ratio at the week 48 and 104 withdrawals is a concern and challenges the hypothesis. In general, increased albumin excretion is indicative of glomerular damage. Considering non-clinical data demonstrating podocyte damage by bardoxolone, the evidence for non-detrimental effect of bardoxolone on the glomeruli do not appear robust.

It is agreed with the applicant that an increase in glomerular filtration could lead to an increase in albuminuria. Notwithstanding, in such case, the excretion of creatinine is expected to raise in parallel, with only minor changes in UACR. In the case of bardoxolone, UACR is raised as well, indicating a relative increase in albuminuria to creatinine excretion. The applicant should discuss whether a direct effect of bardoxolone on the podocytes resulting in an alteration in the filtration barrier can be excluded. Also, the applicant is also asked to discuss whether an increase in UACR has been reported in other products intended for renoprotection.

The applicant has also assessed eGFR changes throughout the study based on quartiles of week 12/baseline UACR. Increases in eGFR of the same magnitude was observed at week 48 and 100 for the quartiles with the highest/lowest change in UACR which may indicate that the UACR increase is unrelated to glomerular damage. However, the scatter in these small groups is high which makes the analysis uncertain.

eGFR Increases

Increased GFR caused by a pharmacological agent can hypothetically cause glomerular damage by increasing the filtration pressure. Direct assessments of filtration pressure cannot be performed clinically. Experimental data from animals suggest that the filtration pressure is unchanged by bardoxolone and the topic is further discussed in the non-clinical assessment report. The applicant has presented data on GFR from the 1- and 2-year withdrawal periods that shows increased GFR compared to placebo in the treatment group (Table 46). In addition, events of the composite of End stage renal disease (ESRD), ≥30% decline from baseline in eGFR, and eGFR <15 mL/min/1.73 m^2 were fewer in the bardoxolone group than placebo (Table 47). This is further discussed in the efficacy section.

Table 46. Change from Baseline in eGFR (mL/min/1.73 m^2) at Last Value on Treatment and at Withdrawal (Analysis Set A and Analysis Set B).

		Analysis Set A		Analysis Set B
		Bardoxolone Methyl (N = 77)	**Placebo (N = 80)**	**Bardoxolone Methyl (N = 153)**
Last Value on Treatment Change from Baseline	n	77	80	152
	LS Mean (SE)	2.41 (1.512)	-8.17 (1.496)	3.40 (1.200)
	p-value vs zero	0.1121	<0.0001	0.0049
	p-value vs Placebo	<0.0001	NA	<.0001
Year 1 Withdrawal Visit Change from Baseline	n	64	69	93
	LS Mean (SE)	0.36 (1.362)	-5.48 (1.326)	-0.27 (1.106)
	p-value vs zero	0.7926	<0.0001	0.8086
	p-value vs Placebo	0.0026	NA	0.0172
Year 2 Withdrawal Visit Change from Baseline	n	48	62	71
	LS Mean (SE)	-3.99 (1.744)	-8.27 (1.539)	-4.03 (1.402)
	p-value vs zero	0.0237	<0.0001	0.0045
	p-value vs Placebo	0.0683	NA	0.4428

Abbreviations: eGFR=estimated glomerular filtration rate; LS=least square; NA=not applicable; SE=standard error; UACR=urinary albumin-to-creatinine ratio
Note: Least square means and p-values are based on an analysis of covariance model for change from baseline to last on-treatment value and separate withdrawal value as the response variable.
In the model, treatment is a fixed effect. Baseline laboratory value, total double-blind treatment duration, and log of baseline UACR are covariates.
Note: Withdrawal period for Year 1 and for Year 2 is defined as the period following the last dose in Week 48 and Week 100, respectively, or the last dose within the year if the patient discontinued study treatment. Test values taken from 14 to 35 days after the last dose and prior to any open-label dosing may be used. The test value analysed is the one taken closest to 28 days following the last dose.
Source: ISS Table 32.1.1; ISS Table 32.1.2

Table 47. Time to End Stage Kidney Disease, eGFR Decline ⩾30%, or eGFR <15 mL/min/1.73 m^2 (Analysis Set A and Analysis Set B)

	Analysis Set A		Analysis Set B
	Bardoxolone Methyl (N = 77)	**Placebo (N = 80)**	**Bardoxolone Methyl (N = 153)**
Time to Event (Days)			
Mean	584.6	623.7	731.7
Standard Error	(12.52)	(19.55)	(13.89)
Hazard Ratio (vs Placebo)	0.49		
Hazard Ratio 95% Confidence Limits	(0.220, 1.090)		NA
ChiSq p-value vs Placebo	0.0803		NA
Censoring Summary			
Patients with Event	9 (11.7%)	18 (22.5%)	20 (13.1%)
Patients Censored	68 (88.3%)	62 (77.5%)	134 (87.6%)

Abbreviations: ChiSq=chi-square; eGFR=estimated glomerular filtration rate; NA=not available; SE=standard error
Note: Patients are censored at the later of the last double-blind treatment end date + 1 day, or the last contact date.
Note: Mean, SE, and censoring summary are based on a Kaplan-Meier analysis. Hazard ratio, confidence limits, and chi-square p-value are based on a Cox proportional hazards model.
Source: ISS Table 34.2.1; ISS Table 34.2.2

3.3.7.5. Laboratory findings

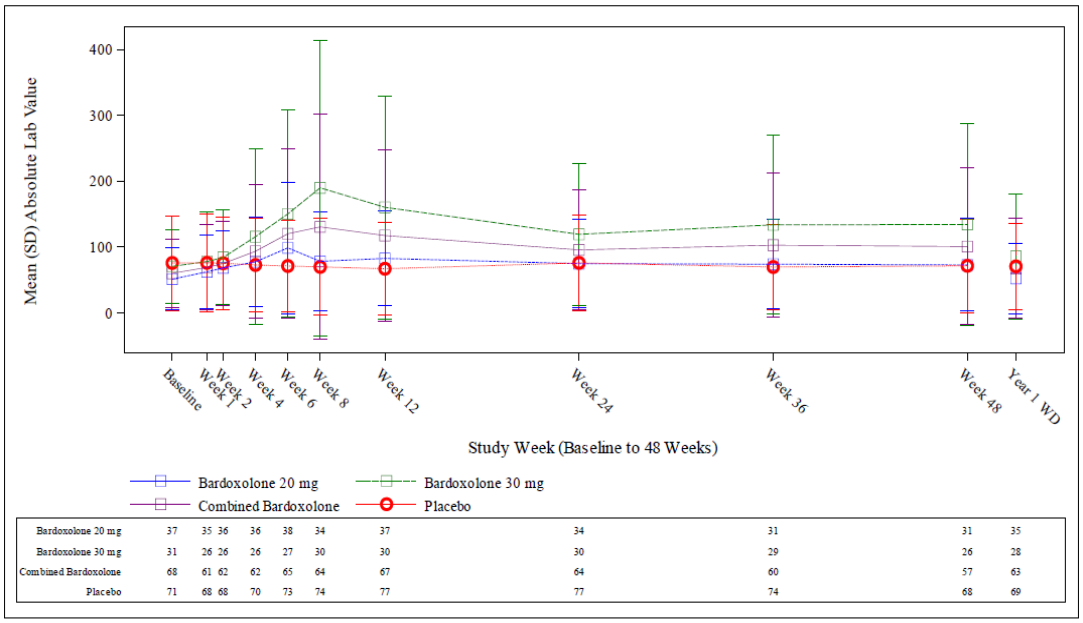
Haematology

Small decreases in haemoglobin, haematocrit, erythrocytes were observed in the bardoxolone group. As discussed previously, there was an imbalance in epistaxis in the pivotal study (Bardoxolone 9.1%; placebo 0%). In the pivotal study, 4 (5%) TEAEs of anaemia were reported in the bardoxolone group (no cases in placebo group). In the previous BEACON study, 8.2% of patients reported TEAE anaemia compared to 4.2% in the placebo group. In addition, 17 SAEs (1.6%) occurred in the bardoxolone group compared to 7 cases (0.6%) in the placebo group. The applicant is requested to present any other cases of bleedings and discuss whether coagulation was affected by bardoxolone (e.g., PK[INR] and aPTT) or whether bardoxolone affects haematopoiesis.

Clinical chemistry

Ferritin

Mean absolute ferritin values from baseline to Week 48 and from Week 64 to Week 100 are shown for Analysis Set A in Figure 24 (baseline to Week 48).



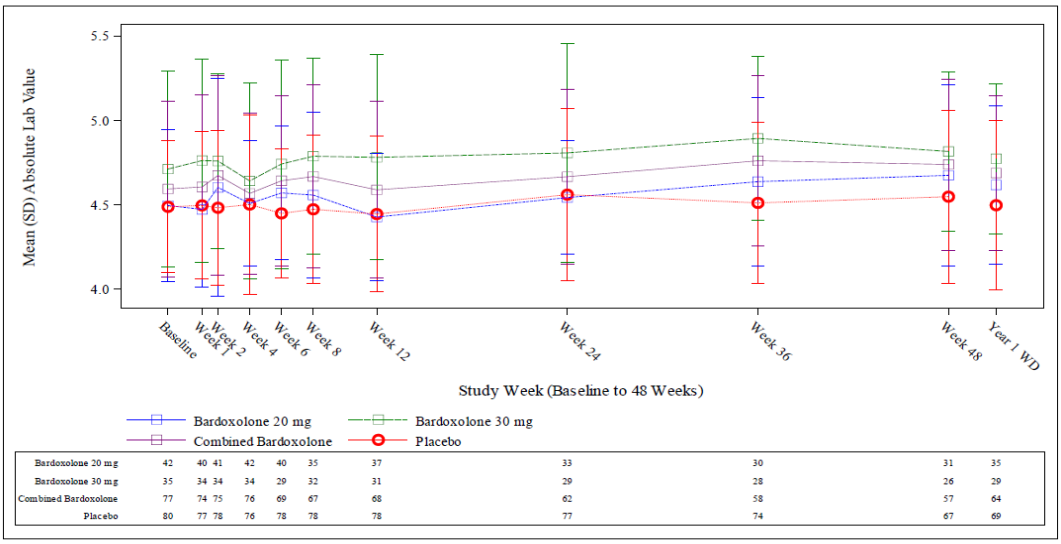
Abbreviations: SD=standard deviation; WD=withdrawal
Source: ISS Figure 4.1.1

Figure 25: Mean Absolute Ferritin (ng/mL), Baseline to Week 48 (Analysis Set A)

Bardoxolone treatment was associated with increased ferritin levels that peaked at week 8 after treatment initiation and stayed elevated throughout the study, which may be due to Nrf2 activation according to the applicant. A higher percentage of bardoxolone methyl-treated patients had one or more on-treatment- high ferritin values compared to placebo-treated patients (21.8% vs 4.9%). For each treatment arm, the applicant is requested to provide information on the number of patients developing x1.5 ULN ferritin (for patients with normal ferritin at baseline). In these patients, it should be analysed whether levels of acute-phase reactants (e.g., C-reactive protein [CRP]) and liver enzymes differs from values in patients with normal ferritin values. Furthermore, the applicant is requested to provide general data on CRP for the pivotal study**.**

Potassium

Mean change in potassium from baseline to Week 48 is shown in Figure 25.



Abbreviations: SD=standard deviation; WD=withdrawal
Source: ISS Figure 4.1.1

Figure 26: Mean Absolute Potassium (mEq/L), Baseline to Week 48 (Analysis Set A)

Bardoxolone treated patients had slightly increased levels of potassium. Also, the frequency of elevated potassium values was higher in bardoxolone methyl-treated patients compared to placebo-treated patients (28 [41.2%] vs 19 [24.4%]). Hyperkalaemia is a complication to renal insufficiency and could further result in cardiac complications (arrhythmia). Although treatment discontinuation due to hyperkalaemia was rare (1/153), there is no recommendation in the SmPC regarding monitoring of potassium despite high frequency of renal insufficiency in the target group. The applicant should clarify the reference value used for classification as "high" and also provide data divided upon relevant potassium levels e.g., ≥5.5; ≥6.0; ≥6.5. In addition, the potential mechanism of action should be discussed. The applicant is invited to include hyperkalaemia among the AESIs and propose adequate monitoring recommendation in PI.

3.3.7.6. In vitro biomarker test for patient selection for safety

Not Applicable

3.3.7.7. Safety in special populations

Effect by age

Among the SOCs, a similar AE profile was seen for patients <18 years as for patients 18-65 years. Nevertheless, there were additional AEs reported in paediatric population (analysis set B): nasopharyngitis, headache, blood CK increased, abdominal pain, weight increased, fluid retention, non-cardiac chest pain, gastroenteritis, viral infection, nausea, dizziness, oropharyngeal pain, proteinuria. The frequency of musculoskeletal and connective tissue disorders was however lower in bardoxolone treated patients <18 years than patients 18-65 years. However, given the few cases and participants, the estimates are in general uncertain.

The clinical experience of bardoxolone treatment in subjects with Alport syndrome younger than 18 years is very limited. The applicant is asked to discuss the potential impact of bardoxolone on growth and development, including sexual development. Furthermore, according to the PIP, a paediatric study (402-C-2001: Open-label, multi-centre study to evaluate pharmacokinetics, safety and efficacy of bardoxolone (methyl) in children from 8 years to less than 17 years of age with Alport syndrome.) is

planned. The applicant is asked to discuss whether the uncertainties regarding safety in adolescents and the planned study should be reflected in the RMP.

No meaningful analysis can be performed on data from patients >65 years given the few numbers. No patients above 75 years were exposed.

Effect by sex

The overall number of TEAEs was similar for male and female participants, respectively. Male participants had an increased frequency of SAEs compared to females; however, the frequency was similar to males receiving placebo. Consequently, the difference in SAEs and differences observed in some SOCs may be related to the generally more severe expression of the disease in male patients.

Effect by ethnicity and race

No conclusions can be drawn regarding race or ethnicity, provided the few participants.

Effect by Body Mass Index Category

For the TEAEs, no clear differences could be seen among the SOCs between the BMI groups. The incidence in SAEs in general was increased for patients with BMI ≥30 kg/m^2, but the incidence was in the same range in both treatment arms. There was a numerical difference in the SOC Renal and urinary disorders (4 cases of end stage renal disease and 1 case of proteinuria). For the placebo treated patients for this subgroup, there were no cases, however the number of placebo-treated patients are few in this subgroup which makes the estimate uncertain.

Consequently, the provided data do not indicate an effect of BMI on the safety profile of bardoxolone.

Effect by baseline CKD Stage (≤2, 3, ≥4)

Incidence of TEAEs were in general similar across groups of CKD stage. There were however some differences, but the estimates are uncertain given the few cases. In bardoxolone treated patients, the incidence of increases in BNP, hyperkalaemia and proteinuria was elevated in patients with CKD stage 3 compared to stage 2. There were very few patients with stage 4 or higher (only patients with eGFR ≥30 mL/min/1.73 m^2 were recruited to the study).

The incidence of SAEs increased with CKD stage but was generally lower in the bardoxolone treated patients. No cases of ESRD occurred in patients with CKD stage 2. In patients with CKD stage 3, there was a numerical imbalance between bardoxolone- and placebo-treated patients (6.6% (4/61) vs. 3.2% (1/31) but the estimate is uncertain given the few cases and limited number of patients.

Baseline UACR category

Patients with baseline UACR >300 mg/g had a higher frequency of SAEs than patients with UACR ≤300 mg/g. All SAEs of ESRD occurred in patients with UACR >300mg/g. Five cases (7.0%) occurred in the bardoxolone group and 2 cases (5.4%) in the placebo group. Given the few numbers, the estimate is uncertain, and no conclusions can be drawn.

Effect by hepatic impairment

Study 402-C-1002 was a Phase 1, multicentre, open-label, non-randomized, single-dose study to assess bardoxolone methyl PK and compare exposures in 34 adult patients with varying degrees of hepatic function (mild, moderate, and severe hepatic impairment) to otherwise healthy subjects. Each received a single oral dose of 20 mg bardoxolone methyl under fasting condition.

Notable exposure differences were found after a single dose of 20 mg bardoxolone in patients with moderate and severe hepatic impairment compared to healthy subjects. This is addressed in the proposed SmPC that do not recommend treatment of this patient group.

3.3.7.8. Immunological events

Not applicable.

3.3.7.9. Safety related to drug-drug interactions and other interactions

Considering the notable effects of itraconazole (strong CYP3A4 inhibitor) coadministration in a dedicated clinical DDI study, use with strong and moderate CYP3A4 inhibitors are contraindicated. If concomitant use of a strong/moderate CYP3A4 inhibitor cannot be avoided, then pause bardoxolone methyl temporarily for the duration of the therapy. Upon discontinuation of a moderate/strong CYP3A4 inhibitor and after 5 plasma half-lives of the CYP3A4 inhibitor, resume bardoxolone methyl at the dose that was used before starting the CYP3A4 inhibitor. Strong and moderate CYP3A4 inducers should be avoided when treating patients with bardoxolone methyl, and alternatives should be considered if possible.

Bardoxolone methyl does not inhibit CYP3A4, CYP2C8, P-gp and BCRP. An OC is raised regarding PK/PD DDI with ACEi/ARBs. For further information regarding DDI, see section 3.3.2. Discussion on clinical pharmacology.

3.3.7.10. Discontinuation due to adverse events

A summary of TEAEs leading to study drug discontinuation is shown in Table 48.

Table 48. Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (Analysis Set A and Analysis Set B)

	Analysis Set A				Analysis Set B		
System Organ Class/ Preferred Term	Bardoxolone Methyl			Placebo	Bardoxolone Methyl		
	20 mg (N = 42)	30 mg (N = 35)	Combined (N = 77)	(N = 80)	20 mg (N = 89)	30 mg (N = 75)	Combined (N = 153)
Number (%) of Patients Reporting TEAEs Resulting in Study Drug Discontinuation	8 (19.0%)	9 (25.7%)	17 (22.1%)	4 (5.0%)	8 (9.0%)	12 (16.0%)	20 (13.1%)
Investigations	5 (11.9%)	4 (11.4%)	9 (11.7%)	0	5 (5.6%)	4 (5.3%)	9 (5.9%)
Alanine aminotransferase increased	4 (9.5%)	2 (5.7%)	6 (7.8%)	0	4 (4.5%)	2 (2.7%)	6 (3.9%)
Aspartate aminotransferase increased	2 (4.8%)	1 (2.9%)	3 (3.9%)	0	2 (2.2%)	1 (1.3%)	3 (2.0%)
Brain natriuretic peptide increased	1 (2.4%)	1 (2.9%)	2 (2.6%)	0	1 (1.1%)	1 (1.3%)	2 (1.3%)
Blood creatinine increased	0	1 (2.9%)	1 (1.3%)	0	0	1 (1.3%)	1 (0.7%)
Gamma-glutamyltransferase increased	0	1 (2.9%)	1 (1.3%)	0	0	1 (1.3%)	1 (0.7%)
Glomerular filtration rate decreased	0	1 (2.9%)	1 (1.3%)	0	0	1 (1.3%)	1 (0.7%)
N-terminal prohormone brain natriuretic peptide increased	1 (2.4%)	0	1 (1.3%)	0	1 (1.1%)	0	1 (0.7%)
Renal and urinary disorders	0	4 (11.4%)	4 (5.2%)	2 (2.5%)	0	7 (9.3%)	7 (4.6%)
End stage renal disease	0	2 (5.7%)	2 (2.6%)	1 (1.3%)	0	5 (6.7%)	5 (3.3%)
Acute kidney injury	0	1 (2.9%)	1 (1.3%)	0	0	1 (1.3%)	1 (0.7%)
Chronic kidney disease	0	1 (2.9%)	1 (1.3%)	0	0	1 (1.3%)	1 (0.7%)
Proteinuria	0	0	0	1 (1.3%)	0	0	0
Gastrointestinal disorders	1 (2.4%)	1 (2.9%)	2 (2.6%)	0	1 (1.1%)	1 (1.3%)	2 (1.3%)
Gastrooesophageal reflux disease	1 (2.4%)	1 (2.9%)	2 (2.6%)	0	1 (1.1%)	1 (1.3%)	2 (1.3%)
Musculoskeletal and connective tissue disorders	1 (2.4%)	1 (2.9%)	2 (2.6%)	0	1 (1.1%)	1 (1.3%)	2 (1.3%)
Muscle spasms	1 (2.4%)	1 (2.9%)	2 (2.6%)	0	1 (1.1%)	1 (1.3%)	2 (1.3%)
General disorders and administration site conditions	0	1 (2.9%)	1 (1.3%)	1 (1.3%)	0	1 (1.3%)	1 (0.7%)
Oedema peripheral	0	1 (2.9%)	1 (1.3%)	1 (1.3%)	0	1 (1.3%)	1 (0.7%)
Metabolism and nutrition disorders	0	1 (2.9%)	1 (1.3%)	0	0	1 (1.3%)	1 (0.7%)
Dehydration	0	1 (2.9%)	1 (1.3%)	0	0	1 (1.3%)	1 (0.7%)
Skin and subcutaneous tissue disorders	1 (2.4%)	0	1 (1.3%)	0	1 (1.1%)	0	1 (0.7%)
Alopecia	1 (2.4%)	0	1 (1.3%)	0	1 (1.1%)	0	1 (0.7%)
Ear and labyrinth disorders	0	0	0	1 (1.3%)	0	0	0
Deafness	0	0	0	1 (1.3%)	0	0	0

Abbreviations: MedDRA=Medical Dictionary for Drug Regulatory Affairs; TEAEs=treatment-emergent adverse events
Note: Adverse event terms were mapped according to MedDRA v21.1.
Source: ISS Table 8.4.1; ISS Table 8.4.2

In general, the rates of TEAEs leading to study drug discontinuation were lower in analysis set B compared to A. For several SOCs, no new additional cases are reported from B than A.

The most common TEAEs leading to study drug discontinuation were in the SOC Investigations. In analysis set A, 7.8% and 3.9% of the bardoxolone patients discontinued due to increases in ALT and AST, respectively, whereas no discontinuations occurred in the placebo group. In analysis set B, the rates were lower (3.9% and 2.0% for ALT and AST, respectively). The clinical studies in Alport patients included criteria for discontinuing patients with ALT/AST elevations above certain levels that depended on accompanying bilirubin levels and clinical symptoms.

A slight imbalance was noted in the SOC renal and urinary disorders for bardoxolone treated patients (4 [5.2%] and 7[4.6%] cases in analysis set A and B, respectively) compared to 2 (2.5%) cases in the

placebo group. However, the estimate is uncertain given the low numbers. In this SOC, 2.6% and 1.3%, respectively, of bardoxolone and placebo treated patients in analysis set A discontinued due to end stage renal disease. In analysis set B, the rate was 3.3%.

Module 2.7.4, section 1.2.1 introductory data on the study drug discontinuations in analysis set B should be corrected as the data presented are not accurate.

Study Drug Interruptions Due to Adverse Events

Similar to study discontinuations, the most common TEAEs leading to study drug interruption in bardoxolone treated patients were in the SOC Investigations. In the pivotal study, study drug interruptions due to increases in ALT (9.1% vs. 0%) and AST (5.2% vs. 0%) were increased compared to placebo. In addition, study drug interruptions due to BNP increased was increased in bardoxolone treated patients compared to placebo (7.8% vs. 2.5%).

Study drug interruptions due to other causes were scattered among the SOCs and no clear pattern could be distinguished.

3.3.7.11. Post marketing experience

Not applicable.

3.3.8. Discussion on clinical safety

Bardoxolone has been investigated in 3 studies on Alport syndrome. The randomized phase 3 Cardinal study (402-C-1603/Phase 3) is the pivotal study where 150 patients (77 Bardoxolone/80 placebo) were studied for 104 weeks. The Cardinal study also involved a preceding phase 2 single arm part where 30 patients were studied for 104 weeks (402-C-1603/Phase 2). The EAGLE study (402-C-1803) is an ongoing open-label extended access phase 3a study in which 96 patients with Alport syndrome is currently enrolled.

The Alport syndrome participants were exposed to bardoxolone according to the proposed titration dosing regimen up to 20-30 mg once daily (based on baseline UACR) and were exposed to the proposed commercial formulation of the medicinal product.

The applicant has divided the data into 4 different analysis sets (A-D) based on study type and the studied conditions.

Analysis set A consists of the pivotal placebo-controlled study in patients with Alport syndrome whereas analysis set B contains safety data from two additional uncontrolled studies (1603/Phase 2 and 1803).

Analysis set C consists of placebo-controlled studies in CKD (i.e. the pivotal RCT on Alport syndrome and two additional RCTs on T2DM and CKD) whereas analysis set D also contains data from single-armed studies and studies on other diseases. Analysis set C has a value for assessment of more rare side effects of bardoxolone, given the larger number of patients included but analysis set D is only briefly discussed given that the included studies differ in design, length and indications.

In total, 153 patients have been exposed to bardoxolone in the proposed indication. In addition, 1230 subjects have been exposed to bardoxolone in CKD and T2D. The median duration of exposure in subject in the proposed indication (Analysis set B) is 1.68 years (0.0-3.2yrs). In total, 106/153 (69%) of the subjects were treated for at least 6 months and 88/153 (58%) for 12 months. 53 of the 153 subjects (35%) were treated for > 96 weeks. In total, the extent of exposure in the proposed indication is low. However, considering a rare disease, the exposure is considered acceptable.

The median age in the bardoxolone and placebo groups in the pivotal study were 43 y (13-65 y) and 43 y (13-70), respectively. No major differences were seen in analysis set B, except that two subjects in the group 66-75 years were exposed to the drug. The proposed indication covers adolescents (12-18 y). In total 21 subjects <18 years have been exposed to bardoxolone methyl with a median age of 15 (13-17) years. Of paediatric patients in analysis set B, 11 (55.0%) were exposed for >48 weeks, and 7 (35.0%) for >96 weeks.

42.1% of subjects receiving bardoxolone were male and 57.9% were female.

Overview adverse events

In the pivotal study (1603/phase 3 [analysis set A)] almost all subjects reported any TEAE in both the bardoxolone (97%) and the placebo group (96%). However, TEAEs related to study drug was more common in the bardoxolone group compared to the placebo group (91% vs 56%). TEAEs with action taken to study drug discontinuation were more common in the bardoxolone group (22%) compared to the placebo group (5%). There is a dose relationship observed regarding incidence of patients with TEAE, incidences of TEAEs leading to study drug interruption/ discontinuation.

Serious TEAEs were reported less frequently in the bardoxolone group (10.4 %) for the combined dose groups than placebo (18.8%). There were very few cases of SAEs related to the study drug across the groups.

No fatal TEAEs was reported in any of the two (A and B) analysis groups. Overall, no major differences were noted when comparing analysis set A and B regarding overall safety.

Among the SOCs, higher frequency of AEs for bardoxolone vs. placebo was observed in the SOC investigations, gastrointestinal disorders, respiratory, thoracic and mediastinal disorders.

Lower frequency of AEs in the bardoxolone group was observed in nervous system disorders, psychiatric disorders, ear and labyrinth disorders, eye disorders and hearing and vestibular disorders. These AEs may be related to common non-kidney manifestations of Alport disease; thus, the decreased incidence may be related to the treatment effect.

Results were similar for the paediatric patients. There were however no serious TEAEs in this group and TEAEs were in general less severe. The precision of the estimate is however limited by the low number of paediatric participants in the study. The clinical experience of bardoxolone treatment in subjects with Alport syndrome younger than 18 years is very limited. The applicant is asked to discuss the potential impact of bardoxolone on growth and development, including sexual development. Furthermore, according to the PIP, a paediatric study (402-C-2001: Open-label, multi-centre study to evaluate pharmacokinetics, safety and efficacy of bardoxolone (methyl) in children from 8 years to less than 17 years of age with Alport syndrome.) is planned. The applicant is asked to discuss whether the uncertainties regarding safety in adolescents and the planned study should be reflected in the RMP.

In the pivotal study, the most reported PT in the bardoxolone treated Alport patients compared to placebo was muscle spasm (49.4% vs. 35.0%) followed by increased ALT (46.7% vs. 2.5%) and increased AST (24.7% vs. 1.3%).

Other common PTs reported in higher frequencies in the bardoxolone group compared to the placebo group are increases in BNP (13.0% vs. 3.8%), weight decreased (13.0% vs. 1.3%), diarrhoea (15.6% vs. 7.5% placebo), hyperkalaemia (14.3% vs. 6.3%), cough (10.4% vs. 3.8%) and epistaxis (9.1% vs. 0%).

In analysis set C, encompassing all double-blind, placebo-controlled studies in CKD, an imbalance was also seen for nausea (18.2% vs. 14%) and vomiting (10.7% vs. 7.6%).

Serious and severe TEAEs and TEAEs with action taken of study drug discontinued tended to be more frequent in the higher bardoxolone dose group but no clear dose-dependency was seen for the PTs. This may be due to not all patients reaching their goal dose and that patients dose escalated/de-escalated their dose during the trial.

For the SAEs, no clear pattern could be distinguished among the PTs, given the low numbers. The 2 most common serious TEAEs in both treatment arms were ESRD (2.6% bardoxolone vs. 2.5% placebo) and pneumonia (0% bardoxolone vs. 2.5% placebo). There is an evident dose dependency observed. Namely, 3.4% in 20mg and 17.3% patients in 30mg bardoxolone group had a SAE in Alport syndrome analysis set. However, the clinical relevance is uncertain given the few cases and that the frequency was lower in the placebo group. In addition, the differences in baseline UACR in the dose groups may have had an impact on adverse events. In the previous BEACON trial on patients with T2D and stage 4 CKD, the overall frequency of SAEs was increased in the bardoxolone arm compared to placebo (33% vs. 27%), mainly driven by a difference in the SOC cardiac disorders (11% vs. 8%). In this SOC, the most frequent PT was cardiac failure (4.8% vs. 3.7%).

No deaths occurred in the studies on patients with Alport syndrome. From the entire analysis set D, 60 fatal cases (2.8%) occurred in bardoxolone treated patients and 31 cases (2.3%) in patients treated with placebo. Most of the fatal cases are from the relatively large BEACON RCT where 44 (3.6%) deaths occurred in the bardoxolone group and 31 (2.5%) cases in the placebo group. Most cases were in the cardiovascular SOC (2.7% bardoxolone vs. 1.8% placebo).

Cardiovascular Safety

The previous BEACON study with bardoxolone in patients with T2D and stage 4 CKD was terminated early due to increase in heart failure events (HR=1.83). The cases occurred within the first weeks of treatment and was possibly due to fluid retention. Elevated baseline BNP and prior hospitalization for heart failure was identified as risk factors, increasing the risk of heart failure by 60%. When the data was analysed for risk factors for fluid overload, the overall frequency of SAEs in patients without these risk factors was similar in the two treatment groups (21.0% bardoxolone vs. 19.7% placebo) however in the SOC cardiac disorders there was still a small imbalance (5.1% [40] vs. 3.8% [31]).

As a safety measure, patients with uncontrolled diabetes, elevated BNP levels and history of cardiac disease (e.g., cardiac insufficiency NYHA III-IV, LVEF <40%, previous hospitalization for heart failure, symptomatic coronary disease) were excluded in the Alport studies.

It is acknowledged that patients with Alport syndrome generally do not have the severe comorbidities and cardiovascular risks associated with T2DM and Stage 4 CKD. However, if bardoxolone is considered as a lifelong treatment, the risk factors in the population will likely increase over time, therefore, this particular risk cannot be ruled out in the Alport population.

According to the applicant, the more advanced kidney dysfunction in the previous BEACON study may have been one of the factors that contributed to the adverse outcome in the bardoxolone group and patients with CKD stage 4-5 were excluded from the Alport studies as a part of the risk mitigation. With this background, it is noted that the proposed wording of the indication in the present SmPC includes subjects with ERSD. The applicant is requested to justify the use of bardoxolone from a safety perspective in subjects with severe renal disease corresponding to CKD 4-5 or to reflect the limitations of the study population in the wording of the indication.

A contraindication has been proposed for patients with NYHA class IV (SmPC section 4.3) and the risk for HF is further reflected in SmPC section 4.4. However, the applicant should justify why only class IV CHF should be contraindicated and that bardoxolone is safe for lower classes of CHF.

AEs compatible with CV risk have been observed, and 30% of patients had AE in SMQ Cardiac failure. Observed cardiac and vascular AEs of interest are BNP increased oedema peripheral, and hypertension.

In the pivotal study (1602/phase 3) increases in mean BNP were observed with bardoxolone methyl treatment relative to baseline through 48 and 100 weeks of treatment. Values trended back to baseline at the Year 1 and Year 2 withdrawal periods, 4 weeks after stopping drug. Mean values remained below the upper limit of normal (<100 pg/L) throughout the study.

Values higher than 200 pg/mL was however observed in 10 individual patients in the treatment group; two of these displayed high values up to 544 pg/mL and 988 pg/mL, respectively. No such cases were observed in the placebo group.

In line with this finding and as discussed above, the PT Brain natriuretic peptide increased was reported in higher frequency of the subject treated with bardoxolone methyl (13.0%) compared to placebo (3.8%) in the pivotal study. In addition, increases in NT-proBNP was reported in a few more cases in the bardoxolone than the placebo group (5.2% vs. 1%).

The applicant speculates that the increase in BNP is due to improvements in metabolic parameters, and cites literature that BNP regulates energy expenditure through processes that are associate with Nrf2 activation. Furthermore, literature indicate that patients with metabolic risk factors have lower BNP, and that bardoxolone is able to improve metabolic processes. In addition, non-clinical data from a mouse model indicates a cardiac protective effect by bardoxolone. From the provided summary, it is not clear whether this data is able to exclude a detrimental effect on cardiac function, as was observed in previous studies on bardoxolone.

Consequently, even though the average increases in BNP by bardoxolone is mild, the substance appears to cause a more pronounced increases in certain individuals. Given that elevated basal BNP levels were identified as a risk factor for development of CHF in previous studies with bardoxolone, the applicant is requested to investigate whether elevated BNP levels were related to AEs within the cardiac disorders SOC, vascular disorders SOC and cardiac failure SMQ.

Within the cardiac failure SMQ, oedema peripheral was the most common PT and the overall frequency was slightly higher in bardoxolone than placebo treated subjects (15.6% vs. 12.5%). One severe case and 6 (3.9%) cases of moderate peripheral oedema were reported in bardoxolone treated subjects while 0 moderate and 1 severe case were reported for placebo treated subjects. Most of them resolved with bardoxolone interruption and/or diuretic treatment while some resolved spontaneously without change of treatment. The frequency of mild cases was similar in bardoxolone and placebo treated subjects (9.8% vs. 11.3%). Thus, the frequency of peripheral oedema was slightly higher in the bardoxolone group, and there were more cases of moderate severity. In addition, there were cases of peripheral swelling reported (bardoxolone: 2 mild, 2 moderate; placebo: 3 mild).

As previously discussed, the BEACON study was terminated early due to increased occurrence of heart failure associated with fluid retention in the treatment group. The observed cases of peripheral oedema/peripheral swelling in the present Alport patients are therefore a concern. The applicant is requested to present narratives from the additional cases of peripheral swelling in Alport patients and also present data on BNP/NT-proBNP levels for all cases of peripheral oedema/peripheral swelling. Furthermore, the applicant is requested to analyse data for risk factors (e.g., baseline CKD stage, use of ACE-Is/ARBs) predisposing to peripheral oedema and rise in BNP, as this would serve to pose contraindications and to develop better patient management and, eventually, limiting the indication. Moreover, it is unclear what the management of treatment would be in the event when patients develop such signs (interruption, discontinuation?). Recommendations should be reflected in the SmPC.

A slight increase in blood pressure (SBP +5.2±10.5 mmHg) was observed in bardoxolone treated subjects in the previous BEACON study when assessed with ambulatory blood pressure monitoring 4 weeks after treatment initiation. Blood pressure was not affected by the bardoxolone treatment in the Alport studies; however, ambulatory blood pressure monitoring was not used. Provided that even small elevations in blood pressure may increase the CV risk if sustained over time, the applicant is requested to discuss the relevance of the finding from the BEACON study in relation to the present Alport population.

Hepatic Safety

From previous studies, there is a known risk for transient elevations of aminotransferases (ALT and AST) and GGT during treatment with bardoxolone. This was also noted in the studies performed in Alport syndrome. In these studies, a transient and dose dependent increase in liver enzymes (AST, ALT, GT and to some extent ALP) with a peak at 6 and 8 weeks respectively was observed. TEAEs for increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) occurred in 46.8% and 24.7%, respectively, in patients on bardoxolone treatment. Frequencies in placebo treated subjects were 2.5% and 1.3%, respectively. 5.2% of bardoxolone patients reported gamma-glutamyltransferase (GGT) increased (1.3% in placebo).

3.9% (3) bardoxolone treated patients (vs. 0% of placebo treated patients) with normal baseline values in the pivotal study displayed increased bilirubin values (>ULN) at some point during the treatment period but none exceeded 2× ULN. According to the laboratory findings, the general effect of bardoxolone however appears to be a slight reduction of the bilirubin concentration.

None of the patients randomized to bardoxolone methyl had maximum ALT or total bilirubin values that met potential Hy’s law criteria.

The applicant speculates that the tissue distribution of ALT and AST is broad and that the observed increases in aminotransferases may be due to pharmacological induction of enzymes also from other sources than the liver, and not related to mechanisms involved in liver injury. The presented mechanistic support is derived from non-clinical data. However, this is questioned as some patients had high levels of ALT which is more specific for the liver compared to AST and rather points to a liver damage at least in some cases, even if no one of the patients randomized to bardoxolone methyl met Hy's law criteria. Therefore, the applicant is requested to discuss any available clinical evidence that support that the observed increases in liver enzymes are derived from other sources than the liver. Furthermore, monitoring of ALT, AST and bilirubin after the first 12 weeks of treatment should be discussed and recommendations amended to SmPC.

In the entire analysis set B, 7 TEAEs within SOC Hepatobiliary disorders were registered in bardoxolone treated patients (no cases in placebo group). 3 cases concerned hepatic steatosis/steatohepatitis, 1 case concerned drug-induced liver injury and 3 cases concerned hepatic function abnormal. Short narratives have been provided but the full narratives are requested. Regarding the cases of steatohepatitis and drug induced liver injury, it is of relevance whether diagnosis was based entirely on increases in liver enzymes or whether there were other signs of liver injury.

The clinical studies in Alport patients included criteria for discontinuing patients with ALT/AST elevations (in total 5 patients were discontinued). The proposed SmPC does not contain any information on ALT/AST monitoring. These criteria may therefore possibly underestimate the risk for liver injury in the clinical studies compared to clinical use. Drug induced liver injury is therefore proposed as an important potential risk (see section 3.4.).

Bardoxolone treatment was associated with increased ferritin levels that peaked at week 8 after treatment initiation and stayed elevated throughout the study, which may be due to Nrf2 activation according to the applicant. A higher percentage of bardoxolone methyl-treated patients had one or

more on-treatment- high ferritin values compared to placebo-treated patients (21.8% vs 4.9%). For each treatment arm, the applicant is requested to provide information on the number of patients developing x1.5 ULN ferritin (for patients with normal ferritin at baseline). In these patients, it should be analysed whether levels of acute-phase reactants (e.g., CRP) and liver enzymes differs from values in patients with normal ferritin values.

Muscle Spasms

Muscle spasms were frequent in both treatment arm, but the frequency was higher in bardoxolone treated subjects compared to placebo. The imbalance was primarily seen in the long term i.e., after more than 12 weeks of treatment. The cases were usually mild, although there were 2 cases of study drug discontinuations. Also, in the previous BEACON study in patients with stage 4 CKD and T2D, muscle spasm was more frequent in bardoxolone treated patients than placebo (42% vs. 15%). The frequency of severe muscle spasm was 5% vs. 1%.

The risk for muscle spasm is currently considered sufficiently reflected in SmPC section 4.8. The applicant considers muscle spasm to be a risk not important for inclusion in the list of safety concerns in the RMP. This is endorsed.

Bardoxolone treated subjects displayed decreased values of creatine kinase (CK) that were sustained throughout the study period. Patients experiencing muscle spasm had similar median decreases from baseline in CK to those seen in patients without muscle spasms.

Provided that hypomagnesemia may be related to muscle spasms and that bardoxolone lowers serum magnesium levels, an analysis of magnesium levels in subjects reporting muscle spasm vs these without muscle spasm should be provided.

Weight Changes

Bardoxolone treated patients displayed a weight decrease that was most pronounced during the first 12 weeks. At week 100, the change was -3.35 vs. 0.16 kg for bardoxolone vs. placebo. Weight loss was more pronounced in patients with high BMI (≥30 kg/m^2) at baseline. No data is available on patients with low BMI (<18.5 kg/m^2).

Weight decreases seem to be dependent on the baseline BMI. Patients with BMI ≥30 kg/m^2 experienced more weight loss over 48 weeks of treatment compared to those with BMI<30 kg/m^2. Mean decreases in weight were apparent by Week 6, continued through Week 12, and tended to plateau between Weeks 12 through Week 48. 7.8% of patients experienced significant weight loss of >7%.

There were 20 paediatric patients treated with bardoxolone in total. Five of these patients had BMI values drop below 18.5 kg/m^2, however, 3 of them gained weight during the study and BMI returned to baseline. However, given the limited clinical experience of bardoxolone treatment in subjects with Alport syndrome younger than 18 years, the applicant is asked to discuss the potential impact of bardoxolone on growth and development, including sexual development.

The applicant comments that the mechanism of the weight loss associated with bardoxolone methyl treatment in humans is not fully understood but speculates that the observed decreases in body weight with bardoxolone methyl may be explained by the Nrf2-dependent improvements in lipid metabolism, fatty acid oxidation, and glycaemic control that have been observed in animal studies with bardoxolone methyl and analogues. Data from the previous BEACON study in patients with stage 4 CKD and T2D, indicated that weight loss was characterized as loss of body fat and not muscle mass (based on reductions in waist circumference and unchanged 24-hour urinary creatinine excretion).

In the studies on Alport patients, there was an imbalance in TEAE diarrhoea (15.6% vs. 7.5%). From the entire analysis set C, an imbalance in nausea (18.2% vs. 14%) and vomiting (10.7% vs. 7.6%) is observed in relation to bardoxolone. The applicant is requested to discuss whether the TEAEs within SOC gastrointestinal disorders is related to the observed weight loss. Furthermore, these TEAEs should be considered for inclusion under section 4.8 of the SmPC.

Infections and Infestations

The proportion of patients with infections and infestations and the time to onset was similar in bardoxolone and placebo treated subjects and involved a large number of PTs. There was a numerical imbalance in cases of upper respiratory tract infections between the groups (14.3% vs. 10% in the placebo group) but it may be a chance finding given the few cases and that it is a common condition. There was also an imbalance in cases of cough (10.4% vs. 3.8% in the placebo group). In the previous BEACON study in patients with stage 4 CKD and T2D, an imbalance for the PT pneumonia was observed (Bardoxolone 5% [51/1092] Placebo 2% [25/1093]). Pneumonia in relation to bardoxolone should be discussed given the imbalance in cough and upper respiratory tract infections in the Alport population.

Changes in urine albumin creatinine ratio (UACR)

Bardoxolone treated subjects displayed increased UACR from week 4 and onwards. UACR tended to decrease after treatment discontinuation.

When data was assessed based on UACR category, a slightly larger proportion of patients on bardoxolone shifted into a higher category than those on placebo (42.9% vs. 35%).

The applicant hypothesizes that the increase in UACR in bardoxolone treated patients is secondary to the increased GFR, due to increased delivery of albumin to the tubules. An analysis of log(UACR)/eGFR ratio for the treatment arms is presented. In this analysis, the ratio is similar at baseline in the two groups. Throughout the first year of treatment, the ratio is numerically lower in the bardoxolone arm compared to placebo. However, during the second year of treatment, the curves seem to overlap, even though the ratio at week 100 is lower in the bardoxolone than the placebo group. Throughout the entire two-year period, the bardoxolone treated subjects demonstrate an increased ratio and the slope of the curve appears similar to that of the placebo group. Also, the apparent increased ratio at the week 48 and 104 withdrawals is a concern and challenges the hypothesis. In general, increased albumin excretion is indicative of glomerular damage. Considering non-clinical data demonstrating podocyte damage by bardoxolone, the evidence for non-detrimental effect of bardoxolone on the glomeruli do not appear robust.

Hyperkalaemia

Bardoxolone treated patients had slightly increased levels of potassium. Also, the frequency of elevated potassium values was higher in bardoxolone methyl-treated patients compared to placebo-treated patients (28 [41.2%] vs 19 [24.4%]). The applicant should clarify the reference value used for classification as 'high' and also provide data divided upon relevant potassium levels, e.g., ≥5.5; ≥6.0; ≥6.5. In addition, the potential mechanism of action should be discussed. The applicant is invited to include hyperkalaemia among the AESIs and propose adequate monitoring recommendation in PI.

3.3.9. Conclusions on clinical safety

In the pivotal study, the most frequently reported PTs in the bardoxolone treated Alport patients compared to placebo were muscle spasms (49.4% vs. 35.0%), increased ALT (46.7% vs. 2.5%) and increased AST (24.7% vs. 1.3%), increases in BNP (13.0% vs. 3.8%), weight decreased (13.0% vs. 1.3%) and diarrhoea (15.6% vs. 7.5%).

Elevations of aminotransferases (ALT and AST) and GGT are known also from previous studies with bardoxolone. No cases of Hy's law have been described but in the Alport studies, there was an imbalance in the SOC Hepatobiliary disorders, and the increases in ALT, AST and GGT was also accompanied by an increase in ferritin. More information is requested on the mechanism and the cases of steatohepatitis.

A previous study with bardoxolone in patients with T2D and stage 4 CKD was terminated early due to an increase in heart failure events, associated with fluid retention. In the Alport studies, patients with certain risk factors were excluded and no cases of heart failure occurred. However, there was an imbalance in cases of increased BNP, and, in addition, the frequency of peripheral oedema was slightly higher in the bardoxolone group, and there were more cases of moderate severity. More information is requested to determine whether these AEs are related to emerging heart failure and that they do not contribute to an increased risk for CV events in the long-term considering the possibly lifelong treatment with bardoxolone.

Bardoxolone treated subjects displayed increased UACR from week 4 and onwards however tended to decrease after treatment discontinuation. Considering that albumin excretion is a well described surrogate marker for glomerular damage, the applicant should discuss whether a direct effect of bardoxolone on the podocytes resulting in an alteration in the filtration barrier can be excluded.

Congestive heart failure has been proposed as an important potential risk by the applicant, which is supported. In addition, drug induced liver injury is proposed as an important potential risk. The applicant is asked to discuss whether the uncertainties regarding safety in adolescents and the planned study should be reflected in the RMP. Given that the carcinogenic potential of bardoxolone methyl has not been studied in animals and the apparent dual role of Nrf2 in cancer, the applicant is asked to consider including malignancy as a potential risk in the RMP.

The safety profile of bardoxolone methyl seems serious, but manageable. Nevertheless, caution is needed as safety data assessment is hampered by a limited safety data pool in Alport syndrome, and by limited long-term data available. True long-term bardoxolone safety data are going to remain very limited as only 50 Alport syndrome patients that previously received bardoxolone were included in the long-term study.

Overall, no special safety issue was observed in the paediatric population. However, the number of adolescents included in the clinical development program is small, precluding any definite conclusions.

Considering the intended indication, the most worrisome observations are the increase in albuminuria and the possible CV risk.

Besides renal function monitoring, there is a need for monitoring hepatic function, body weight, serum potassium (not presently agreed with the applicant), and for signs and symptoms of CHF.

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	CHF secondary to fluid overload Safety with concomitant use with strong/moderate CYP3A4 inhibitors
Important potential risks	Potential loss of efficacy with concomitant use with strong/moderate CYP3A4 inducers
Missing information	Use in pregnant and lactating women Long-term use

3.4.1.1. Discussion on safety specification

The CHMP considers that the data presented in the RMP module SI-SIV is largely acceptable.

The risk for congestive heart failure secondary to fluid overload is based on results from studies performed in patients with T2D and stage 4 CKD i.e., a different indication than Alport syndrome. However, since the risk is associated to, and known for, the substance and both diseases are related to a decreased filtering function of the kidney, it is appropriate to include the risk as a safety concern in the RMP for bardoxolone methyl.

A category 3 PASS has been proposed by the applicant to further evaluate the risk for CHF (see PRAC Rapp AR).

As previously discussed, the applicant should justify the safe use of bardoxolone in subjects with all grades of symptomatic cardiac failure or include these subjects in the contraindication, given that subjects with NYHA III-IV were excluded from the pivotal study to reduce the potential for bardoxolone methyl-induced fluid overload. The proposed SmPC proposes a contraindication for subjects with NYHA IV only.

The risk "concomitant use with strong/moderate CYP3A4 inhibitors" is well characterized and properly addressed in the proposed SmPC. The risk is not considered to affect the benefit-risk profile. Consequently, the risk can be removed as a safety concern.

The proposed SmPC states that concomitant administration of moderate or strong CYP3A4 inducers should be avoided. Given that the risk "Potential loss of efficacy with concomitant use with strong/moderate CYP3A4 inducers" is not considered to affect the benefit-risk profile, and the risk can be removed as a safety concern.

Bardoxolone treatment is associated with increases in ALT, AST, GGT and ferritin. No cases of Hy's law have been observed and the applicant speculates that the observed increases in liver biomarkers may have extrahepatic origin. However, given that the exposed number of patients is relatively limited and that a few events potentially reflecting liver injury (liver steatosis [n=3] and drug induced liver injury [n=1]) have been registered in bardoxolone treated subjects, "drug induced liver injury" is proposed as an important potential risk.

According to the PIP, a paediatric study (402-C-2001: Open-label, multi-centre study to evaluate pharmacokinetics, safety and efficacy of bardoxolone (methyl) in children from 8 years to less than 17 years of age with Alport syndrome.) is planned. The applicant is asked to discuss whether the uncertainties regarding safety in adolescents and the planned study should be reflected in the RMP.

The carcinogenic potential of bardoxolone methyl has not been studied in animals. The applicant has provided a carcinogenicity risk assessment based on a weight of evidence approach. There was no

imbalance in malignancies in the clinical studies, however given the apparent dual role of Nrf2 in cancer, the applicant is asked to consider including malignancy as a potential risk in the RMP.

In addition, pending responses to the LoQ, the testes and epididymides effects observed in the 9-month repeated-dose toxicity in dogs should be included in the RMP.

3.4.1.2. Conclusions on the safety specification

Having considered the data in the safety specification it is considered that the following issues should be addressed:

It is considered that drug induced liver injury should also be a safety concern.

It is considered that "concomitant use with strong/moderate CYP3A4 inhibitors" and "potential loss of efficacy with concomitant use with strong/moderate CYP3A4 inducers" should not be safety concerns.

3.4.2. Pharmacovigilance plan

The proposed Pharmacovigilance Plan consists of routine pharmacovigilance activities; this will include the use of Standard Medical Follow-up Questionnaires (SMFQ) for the risks of 'CHF (Congestive Heart Failure) secondary to fluid overload', 'safety with concomitant use with strong/moderate CYP3A4 inhibitors', and 'potential loss of efficacy with concomitant use with strong/moderate CYP3A4 inducers. Those SMFQs will also be used for the missing information on 'Use in pregnant and lactating women' and 'Pregnancy Exposure in Utero'.

Furthermore, expedited Pharmacovigilance monitoring will be applied for CHF secondary to fluid overload: CHF grade 3 and 4, death related to CHF.

The applicant is proposing a safety registry for 5 years which will provide longitudinal safety data after commercial launch. This registry will focus mainly on safety data with a few clinical outcomes including kidney function as determined by eGFR, kidney failure (e.g., kidney transplantation or dialysis) and mortality rate and causes. The protocol will be established and submitted for review to the health authority for feedback prior to the initiation of the registry. Registry at present is proposed to include subjects on commercial bardoxolone methyl. This will provide long term data.

Proposed size of the registry at present is 500 total subjects prescribed bardoxolone methyl. The safety data on yearly basis will be communicated to the health authority.

3.4.2.1. Summary of planned additional PhV activities from RMP

Table 49. On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Category 3 - Required additional pharmacovigilance activities				
An obser-vational, Post-marketing Registry Bardoxolone Methyl in Patients with Alport Syndrome Status: Planned	Primary Objective: To evaluate the real-world safety of bardoxolone methyl in patients with Alport syndrome.	Long term safety of bardoxolone methyl CHF secondary to fluid overload	Annual updates	Data will be reviewed annually, and reports will be submitted to applicable Regulatory Agencies.

Given the proposed revision of the list of safety concerns by the CHMP, the applicant is requested to adequately update all parts of the RMP and propose appropriate pharmacovigilance activities and risk minimisation measures.

The questionnaires in Annex 4 have to be provided in the next version of the RMP.

The applicant included one study as additional pharmacovigilance activities in the pharmacovigilance plan. The applicant proposed a post-marketing safety study using a registry. A PASS to monitor and further characterise the safety of Bardoxolone methyl using a Patient Registry is strongly supported. Inclusion of this study as a category 3 study is accepted.

It is currently unclear which registry the applicant intends to use. The applicant should comment on the suitability (are all the current safety concerns and missing information registered) and availability of existing Alport Registries, such as the European Alport registry, or whether the applicant aims to start a new registry.

The proposed registry-based study should be revised based on the following comments:

- The primary objectives require a revision in line with the safety outcomes of interest based on the further revision of the list of safety concerns following the CHMP discussion. The applicant is requested to discuss whether it is feasible to further characterize these safety concerns and to provide meaningful results. To this end, the applicant is requested to discuss availability, quality and completeness of data elements needed for the study, and the feasibility of introducing any additional data collection if required. In addition, the applicant should justify the inclusion of the three exploratory objectives, as these are not related to safety concerns in the RMP.

- The applicant is requested to justify the proposed study size of 500 patients. Also, considering the proposed milestones, the total duration of the registry study of 5 years needs further justification. Considering the expected long-term use of the product, and risk of Cardiovascular events (see

discussion clinical safety, CHMP Rapp), the applicant is requested to propose and justify a sufficient minimal long-term follow-up time for each patient.

- The applicant should include an updated version of the study synopsis in the Annex 3 of the RMP.

- The study protocol should be submitted within 3 months after marketing authorisation. The milestones should be updated accordingly.

3.4.2.2. Overall conclusions on the PhV Plan

The CHMP and PRAC, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is not sufficient to identify and characterise the risks of the product. The applicant should propose appropriate PhV activities for each of the newly included safety concerns following CHMP comments on the safety concerns. The proposed registry-based PASS is strongly supported, but requires explanations by the applicant with regard to sample size and duration of the study.

3.4.3. Risk minimisation measures

Table 50. Description of routine risk minimisation measures by safety concern.

Safety concern	Routine risk minimisation activities
Important identified risk: CHF secondary to fluid overload	**Routine risk communication:** SmPC section 4.4, and 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Section 4.3 Bardoxolone methyl is contraindicated in patients with severe CHF (New York Heart Association (NYHA) class IV). Section 4.4: Patients should be informed about the signs/symptoms of CHF (e.g., sudden weight gain (≥ 2 kg in 3 days), peripheral oedema or shortness of breath) and when to seek medical attention. Patients should be advised to monitor their weight regularly. (See sections 4.2 and 4.8). **Other routine risk minimization measures beyond the product labeling:** Restricted medical prescription
Important identified risk: Safety with Concomitant use with strong/moderate CYP3A4 inhibitors	**Routine risk communication:** SmPC Section 4.5, 5.2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Section 4.2: Patients should be advised to avoid grapefruit and grapefruit juice during treatment. Section 4.3: Concomitant administration of moderate or strong CYP3A4 inhibitors is contraindicated. Section 4.5: Concomitant administration of moderate (e.g., ciclosporin, ciprofloxacin, fluconazole, fluvoxamine) or strong (e.g., clarithromycin, grapefruit / grapefruit juice, itraconazole, ketoconazole) CYP3A4 inhibitors significantly increases systemic exposure to bardoxolone methyl and is contraindicated during treatment with IMBARKYD. Concomitant administration of weak CYP3A4 inhibitors results in minimal changes to

	bardoxolone methyl systemic exposure. **Other routine risk minimization measures beyond the product labeling:** Restricted medical prescription
Important potential risk: Potential loss of efficacy with concomitant use with strong/moderate CYP3A4 inducers	**Routine risk communication:** SmPC Section 4.5 and 5.2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Section 4.2: Patients should be advised to avoid St. John's Wort (*Hypericum perforatum*) during treatment. Section 4.4: Concomitant administration of moderate or strong CYP3A4 inducers should be avoided whenever possible during treatment. When the moderate or strong CYP3A4 inducer is discontinued, resume treatment after at least 5 half-lives of the CYP3A4 inducer at the dose of bardoxolone methyl previously used (See section 4.5). Section 4.5: Concomitant administration of moderate (e.g., efavirenz, etravirine, phenobarbital, primidone) or strong (e.g., phenytoin, rifampicin, St. John's wort (*Hypericum perforatum*)) CYP3A4 inducers significantly reduces systemic exposure to bardoxolone methyl and, therefore, results in decreased efficacy. **Other routine risk minimization measures beyond the product labeling:** Restricted medical prescription
Missing information: Use in pregnant and lactating women	**Routine risk communication:** SmPC section 4.6, 5.3 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Section 4.6: Pregnancy: There are no adequate data on the use of bardoxolone methyl in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of bardoxolone methyl during pregnancy and in women of childbearing potential not using contraception. Breast-feeding: It is not known whether bardoxolone methyl is excreted in human milk. Available toxicological data in monkeys have shown excretion of bardoxolone methyl in milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from bardoxolone methyl therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. **Other routine risk minimization measures beyond the product labeling:** Restricted medical prescription
Missing information: Long-term use	**Routine risk communication:** SmPC section 5.1 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the product labeling:**

	Restricted medical prescription

The section on routine risk minimisation measures should be updated based on the CHMP discussion on the summary of safety concerns.

No additional risk minimisation measures have been proposed by the applicant. However, depending on the CHMP discussion on the summary of safety concerns, the RMP including the risk minimisation measures may require further amendments.

3.4.4. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.1 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed assessment report and in the list of questions in section 6.3.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3.5.2. Periodic Safety Update Reports submission requirements

To be completed later in the procedure.

4. Non-Conformity with agreed Paediatric Investigation Plan

Not Applicable

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

The proposed indication for Imbarkyd is *Treatment of chronic kidney disease (CKD) caused by Alport syndrome in adults and adolescents aged 12 years and above*.

Alport syndrome is a rare, inherited progressive form of glomerular disease, often associated with sensorineural hearing loss and ocular abnormalities. Studies in the EU indicate that Alport syndrome is observed in approximately 1:50,000 live births and that X-linked disease among males is observed in 1:17,000 live births.

Alport syndrome is caused by mutations in three genes encoding the α3, α4, and α5 chains of Type IV collagen, which is a major constituent of the glomerular basement membrane (GBM) in the kidney. The defective Type IV collagen leads to splitting in the GBM and loss of integrity, triggering abnormal leakage of proteins (e.g., albumin) and excessive protein reabsorption in the proximal tubules, that result in glomerulosclerosis and tubulo-interstitial fibrosis.

The different mutations result in different inheritance patterns. The most common form of Alport Syndrome is the X-linked form, representing roughly 55-70% of all cases.

The severity of disease differs by the inheritance pattern and the nature of the causative mutation. As per data from National Organization for Rare Disorders/Alport Syndrome Foundation, approximately 50% of untreated males with X linked Alport syndrome (XLAS) develop kidney failure by age 25. The lifetime risk for End Stage Renal Disease (ESRD) in male subjects with XLAS is 100% compared to 25% in female subjects. The lifetime risk for ESRD in both males and females is 100% in autosomal recessive (ARAS) and 20% in autosomal dominant (ADAS)

The aim of the therapy is to slow the progression to ESRD.

5.1.2. Available therapies and unmet medical need

There are no therapies specifically targeting the renal impairment in Alport syndrome at this time point.

Current treatment recommendations for the decline of kidney function in patients with Alport syndrome include treatment with inhibitors of the RAAS pathway (e.g., ACEi and/or ARBs).

Imbarkyd is not intended as an alternative treatment to RAAS inhibition and has been administered both with and without RAAS inhibition in the Alport studies. There is a strong unmet need for additional therapies targeting the rapid deterioration of renal function in Alport syndrome with its high risk of developing ESRD at a young age.

5.1.3. Main clinical studies

Clinical data were mainly obtained from three clinical studies: Study 1603/Phase 3 (pivotal), Study 1603/Phase 2, and Study 1803. Supportive data were presented from studies with bardoxolone in subjects with CKD due to other conditions, mainly diabetes.

Study 1603/Phase 3 was a double-blind, randomised, placebo-controlled multicentre study in male and female patients aged 12 to 70 years with Alport syndrome conducted in the US, EU, Australia and Japan. Study 1603/Phase 3 included 77 subjects in the bardoxolone arm and 80 subjects in the placebo arm. The study is completed.

Study 1603/Phase 2 was an open-label, uncontrolled multicentre study in male and female patients aged 12 to 70 years with Alport syndrome conducted in the US. The study included 30 subjects. The study is completed.

Study 1803 is an ongoing long-term study eligible for subjects from 1603/Phase 2 or 1603/Phase 3 (placebo and bardoxolone) of Study 1603. The primary objective of Study 1803 was long-term safety. As of the 18 January 2021 interim database lock date, 96 patients were had been enrolled in Study 1803. Data on eGFR is collected in the study. Study 1803 is planned to continue until bardoxolone is commercially available.

5.2. Favourable effects

Change from Baseline in eGFR at Week 48 and Week 100

Change from Baseline in eGFR at Week 48 and Week 100 was the primary endpoint in Study 1603/Phase 3 and a secondary endpoint in Study 1603/Phase 2

1603/Phase 3 Week 48 (ITT population)

In the placebo arm (n=71), the LS mean (SE) change from baseline was -4.77 (1.248) mL/min/1.73 m^2 (97.5% CI -7.60, -1.95), p-value vs baseline 0.0002.
This indicates a continued deterioration of renal function during the first 48 weeks of treatment in line with the historical eGFR deterioration (-4.9 mL/min/1.73 m^2 per year over the last five years in this treatment arm)

In the bardoxolone arm (n=66), the LS mean (SE) change from baseline was +4.71 (1.307) mL/min/1.73 m^2 (97.5% CI 1.75, 7.68), p-value vs baseline 0.0004.

The LS Mean Difference (SE) bardoxolone vs placebo was 9.49 (1.813) mL/min/1.73 m^2 (97.5% CI 5.38, 13.60), p<0.0001

1603/Phase 3 Week 100 (ITT population)

In the placebo arm (n=73), the LS mean (SE) change from baseline was -8.45 (1.478) mL/min/1.73 m^2 (95% CI -11.38, -5.53), p-value vs baseline <0.0001.
The deterioration of renal function thus continued at approximately the same rate as during the first year in the study.

In the bardoxolone arm (n=65), the LS mean (SE) change from baseline was -0.81 (1.556) mL/min/1.73 m^2 (95% CI -3.89, 2.27), p-value vs baseline 0.6043.
The improvement in renal function seen during the first 48 was not sustained during the second year of treatment.

The LS Mean Difference (SE) bardoxolone vs placebo was 7.65 (2.144) mL/min/1.73 m^2 (95% CI 3.41, 11.89), p=0.0005
This indicates that despite the deterioration in renal function between Week 48 and Week100 in the bardoxolone arm, renal function was still better in the bardoxolone versus the placebo arm.

Subgroup analysis 1603/Phase 3

A prespecified subgroup analysis was performed for the primary analysis at Week 100. The subgroups analysed included age (<18, ≥18 years), gender, baseline UACR (≤300 mg/g, >300 mg/g), use of RAAS inhibition and baseline eGFR ≤ 60, >60 mL/min/1.73 m2) and genetic subtype (XLAS, non-XLAS).
In all subgroups, the point estimate favours bardoxolone, although not always significantly.

1603/Phase 2 Week 48 (ITT population n=28)

The LS mean (SE) change from baseline was 7.40 (1.945) mL/min/1.73 m^2 (95% CI 3.40, 11.39), p-value vs baseline 0.0008.
This indicates a somewhat larger increase in renal function during the first 48 weeks of treatment compared to the bardoxolone arm of the 1603/Phase 3 study

1603/Phase 2 Week 100 (ITT population n=23)

The LS mean (SE) change from baseline was 4.28 (1.748) mL/min/1.73 m^2 (95% CI 0.84, 7.72), p-value vs baseline 0.015.
As in the bardoxolone arm of the 1603/Phase 3 study, renal function deteriorated on treatment between Week 48 and Week 100. As opposed to the bardoxolone arm of the 1603/Phase 3 study, eGFR remained significantly higher than baseline in the 1603/Phase 2 study.

Change from Baseline in eGFR at Week 52 and Week 104

Change from Baseline in eGFR at Week 52 and Week 104 after four weeks off treatment was the key secondary endpoint in Study 1603/Phase 3 and an exploratory endpoint in Study 1603/Phase 2. The off-treatment period was included to assess the possibility of negative long-term effect of bardoxolone on glomeruli, e.g., accelerated fibrosis. The duration of the off-treatment period was chosen to allow acute pharmacodynamic effects on glomerular function to washout.

1603/Phase 3 Week 52 (ITT population)

In the placebo arm (n=68), the LS mean (SE) change from baseline was -6.08 (1.243) mL/min/1.73 m^2 (97.5% CI -8.87, -3.29), p-value vs baseline 0.0001.
As expected, the off-treatment period did not affect the rate of deterioration in the placebo arm.

In the bardoxolone arm (n=66), the LS mean (SE) change from baseline was +4.71 (1.307) mL/min/1.73 m^2 (97.5% CI -3.80, 1.81), p-value vs baseline 0. 4273.
This indicates a marked deterioration of renal function during the four weeks off-treatment compared to the slower fall in eGFR Week 12-48.

The LS Mean Difference (SE) bardoxolone vs placebo was 5.09 (1.656) mL/min/1.73 m^2 (97.5% CI 1.37, 8.80), p=0.0021
Despite the accelerated fall in eGFR in the bardoxolone arm. The treatment difference between the arms remained at Week 52.

1603/Phase 3 Week 104 (ITT population)

In the placebo arm (n=69), the LS mean (SE) change from baseline was -8.84 (1.353) mL/min/1.73 m^2 (95% CI -11.49, -6.19), p-value vs baseline <0.0001.
There was no relevant change from baseline in eGFR between W52 and Week 104 in the placebo arm.

In the bardoxolone arm (n=56), the LS mean (SE) change from baseline was -4.52 (1.395) mL/min/1.73 m^2 (95% CI -7.26, -1.79), p-value vs baseline <0.0012.
This indicates a similar fall in eGFR during the second off-treatment period as during the first. At Week 104, eGFR in the bardoxolone arm was significantly lower than at baseline.

The LS Mean Difference (SE) bardoxolone vs placebo was 4.26 (1.876) mL/min/1.73 m^2 (95% CI 0.58, 7.94), p=0.0232
Despite the deterioration in renal function between Week 52 and Week 104 in the bardoxolone arm, renal function was still better in the bardoxolone versus the placebo arm at Week 104.

1603/Phase 2 Week 52 (PP population n=24)

The LS mean (SE) change from baseline was 3.96 (1.881) mL/min/1.73 m^2 (95% CI 0.05, 7.87), p-value vs baseline 0. 0.0476.

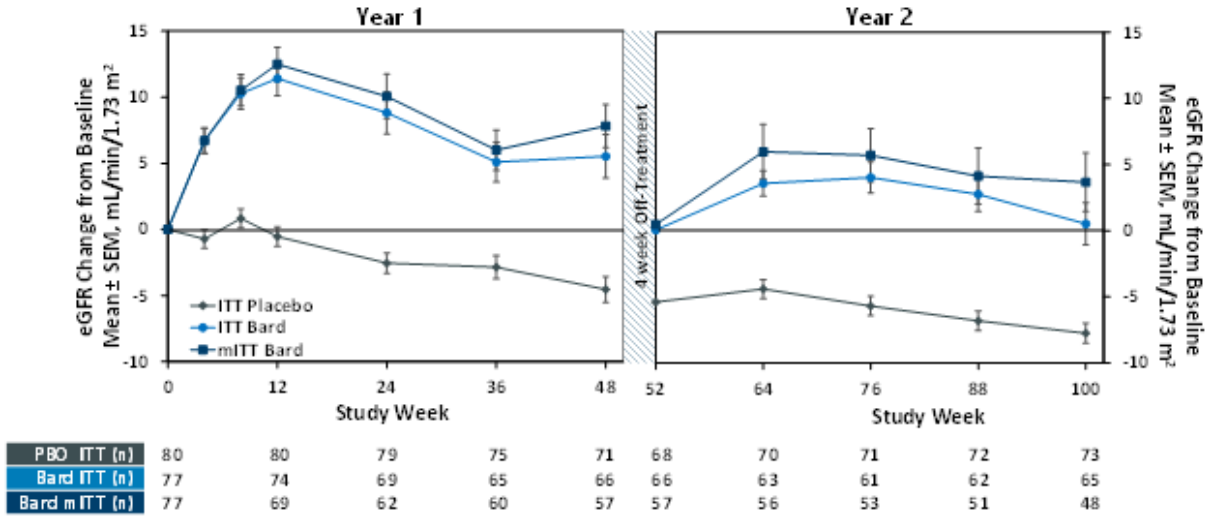
1603/Phase 2 Week 104 (PP population n=23)

The LS mean (SE) change from baseline was -1.75 (1.867) mL/min/1.73 m^2 (95% CI -5.43, 1.92), p-value vs baseline 0. 0.349.

The result in the 1603/Phase 2 study at Week 52 and Week 104 were consistent with the results from the 1603/Phase 3 study.

Continuous eGFR (eGFR Over Time)

Continuous eGFR (eGFR Over Time) was an exploratory endpoint in the 1603/Phase 3 study



Abbreviations: Bard=bardoxolone methyl; eGFR=estimated glomerular filtration rate; ITT=intent-to-treat; mITT=modified intent-to-treat; PBO=placebo; SEM=standard error of the measure

Figure 27: Descriptive Summary of Change from Baseline in eGFR for Bardoxolone Methyl Versus Placebo (ITT and mITT Population) (Study 1603 Phase 3)

Study 1803

Twenty-seven patients have completed through Week 48 in Study 1803 and 19 of these patients had approximately 3 years of exposure to bardoxolone methyl (48 weeks of exposure in Study 1803 and 2 years of the exposure in a prior qualifying study)

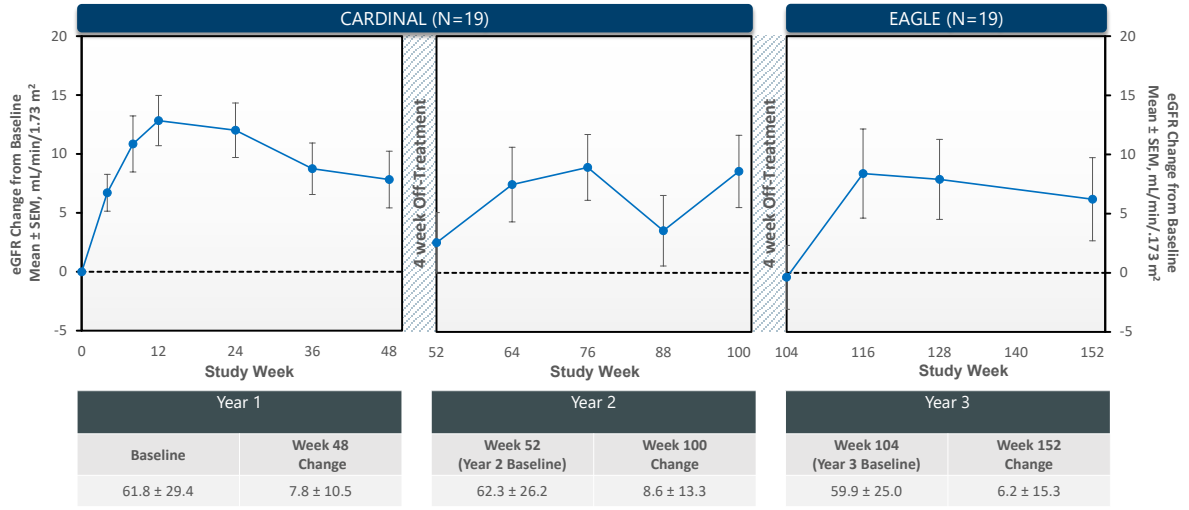


Figure 28: Study 1803: Change from Baseline in eGFR after 1, 2, and 3 Years of Treatment with Bardoxolone Methyl (19 Patients with 3 Year Data)

5.3. Uncertainties and limitations about favourable effects

The generation of the study results is questionable based on the fact that over 50% of potentially eligible patients were not suitable for inclusion in this single pivotal trial (371 screened, 214 excluded of which 184 failed to meet the inclusion criteria). This should be further discussed.

There were no dose finding studies in subjects with Alport syndrome. Dosing in Study 1603 is mainly based on Study 0902 in diabetic patients. As opposed to the large Phase 3 study 0903 (BEACON) in subjects with type 2 diabetes (T2DM) and severe chronic impairment (CKD 4), different target doses

were used in Study 1603 based on baseline urinary albumin/creatinine ratio (UACR) (UACR ≤300 mg/g: 20 mg, >300 mg/g: 30 mg). The applicant justifies this with results from Studies 0902 and 0903. Data supporting the differentiated dosing needs to be presented in a more concise and assessable way.

The degree of comparability between patients with different diseases (CKD in T2DM, diabetic nephropathy vs Alport syndrome) with respect to pharmacokinetic parameters influencing the optimal dose is unclear; however important differences seem plausible. The dosing schedule proposed for marketing is more gradual compared to the dosing schedule tested in Phase 2/3 trial. This also means that the dosing schedule proposed for marketing has not been tested in any clinical trial in the intended indication. These issues should be further justified.

The combined pool of patients younger than 18 who were studied in the pivotal trial of Alport syndrome indication and were administered bardoxolone is very limited, even for an orphan indication. The applicant should justify how the efficacy and safety results from CARDINAL Phase 3 can be applied to the broader adolescent population with Alport syndrome and clarify future plans regarding assessments of efficacy and growth and development in this population.

In the primary and secondary analyses of the 1603/Phase 3 study, eGFR collected after starting dialysis or after receiving a kidney transplant is considered invalid and is treated as missing and the primary analysis of efficacy is based on an assumption of missing at random (MAR). Starting dialysis or receiving a kidney transplant is an indication of a permanently failed kidney function and values after such event should be imputed with a worst possible score. Whether eGFR collected after starting dialysis or after receiving a kidney transplant was included in the analysis in the 1603/Phase 2 study is not clear and should be clarified. If such values were excluded from analysis, new analysis with a worst-case imputation should be provided.

Additional statistical uncertainties concern for example the protection of the type I error, handling of missing values due to COVID-19 and adjustment for baseline covariates. Furthermore, a clarification on whether subjects were actually excluded from the primary analysis and discontinuations over time in the form of Kaplan-Meier curves are requested**.**

The applicant has presented an extensive justification to support the length of the washout period after Week 48 and Week 100. The data supporting the 30-day-window is still limited and with high variable quality. There are however indications that the 30 days off-treatment may not be sufficient for a complete washout of pharmacodynamic effects. The visit window for the Week 52 and Week 104 analyses was broad, allowing test sampling after as little as two weeks off treatment. The purpose of the analysis of the secondary endpoints based on week 52 and week 104 data was to examine any remaining effect after 4 weeks of treatment discontinuation. Hence a supplementary analysis should be performed on observed values without imputation including only values at least 4 weeks after last dose of study treatment.

Subjects with CKD 4-5 (eGFR <30 mL/min/1.73 m^2) were excluded from Study 1603 for safety reasons following the early termination of the BEACON study due to an imbalance in heart failure events in subjects with type 2 diabetes and CKD 4 (see also section 5.4. below). As a consequence, neither efficacy nor safety was studied in this subpopulation. Notwithstanding, the proposed indication includes all stages of chronic renal impairment. This needs further justification. Available data does not indicate a disease modifying effect but rather that the major benefit with bardoxolone treatment is in fact rapid pharmacodynamic effects which, if caused by an increase in intraglomerular pressure, could lead to accelerated damage to the glomeruli and accelerated progression to ESRD. This needs further discussion. Clinical relevance of the transient (i.e., steep decrease in eGFR after treatment withdrawal) rise in eGFR should be discussed.

The significantly higher proportion of patients from Phase 2 compared to Phase 3 progressing to ESRD requires clarification.

Concerns about study conduct and integrity of data have raised. In the Data Monitoring Committee (DMC) Meeting minutes, it is seen that the Sponsor decided to unblind themselves after completion of the first year of treatment despite this was discouraged by the DMC and also made the Year 1 data publicly available without proper communication with the DMC. The Sponsor did not agree to re-consent patients following the publication of Year 1 results. Final meeting minutes seem to be missing. Furthermore, extensive protocol changes were made well into the duration of the study and over 50% of the subjects reported at least one major protocol deviation.

Concerns are raised regarding study conduct that have the potential of affecting the integrity of the study and validity of the data acquired. Extensive protocol changes were made well into the duration of the study. Major protocol deviations were recorded in over 50% of the patients. Over 20% of participants had a protocol deviation regarding informed consent. Over 20% of participants had protocol deviations which included failure of informing the Investigator of weight gain and failure of having an unscheduled assessment and/or increasing BNP or transaminases. This is of concern, as both fluid retention and elevated liver enzymes are adverse events of special interest for bardoxolone. The applicant should inform if a pattern in these deviations was observed (i.e., clustering in any particular study centre or at any particular timepoint). If any of these deviations led to subsequent permanent withdrawal of the informed consent should also be stated. In addition, the applicant should present a list of all AEs recorded in patients who had a major protocol deviation related to failure of informing PI of weight gain and should explain steps taken to ensure safety of those patients.

There is an additional number of other efficacy concerns in need of further clarification.

The SmPC needs to be updated in several areas.

5.4. Unfavourable effects

In total, 153 patients have been exposed to bardoxolone in the intended indication. In addition, 1230 subjects have been exposed to bardoxolone in CKD and T2D. The median duration of exposure in subject in the intended indication is 1.68 years (0.0-3.2yrs). In total, 106/153 (69%) of the subjects in the intended indication were treated for at least 24 weeks and 88/153 (58%) for at least 48 weeks. 53 of the 153 subjects (35%) were treated for at least 96 weeks.

The number of TEAEs were balanced for bardoxolone (97%) and placebo (96%); however, the incidence of treatment related TEAEs was increased for bardoxolone (91%) compared with placebo (56%). The most commonly reported TEAEs that were reported more frequently for bardoxolone than for placebo were muscle spasm (49.4% vs. 35.0%), increased alanine aminotransferase (ALT) (46.7% vs. 2.5%), increased aspartate aminotransferase (AST) (24.7% vs. 1.3%), increased brain natriuretic peptide (BNP) (13.0% vs. 3.8%) and weight decreased (13.0% vs. 1.3%).

Serious TEAEs were reported less frequently for bardoxolone (10.4 %) compared with placebo (18.8%). No fatal TEAEs was reported. For the SAEs, no clear pattern could be distinguished among the PTs, given the low numbers. The most common serious TEAE was ESRD (2.6% bardoxolone vs. 2.5% placebo).

In the pivotal study, increases in mean values of brain natriuretic peptide (BNP) were observed with bardoxolone methyl treatment relative to baseline through 48 and 100 weeks of treatment. Values trended back to baseline at the Year 1 and Year 2 withdrawal periods, 4 weeks after stopping the drug. Mean values remained below the upper limit of normal (<100 pg/L) throughout the study. Values higher than 200 pg/mL was however observed in 10 individual patients in the treatment group: two of

these displayed high values up to 544 pg/mL and 988 pg/mL, respectively. No such cases were observed in the placebo group. The PT BNP increased was reported in higher frequency of the subject treated with bardoxolone methyl (13.0%) compared to placebo (3.8%) in the pivotal study. In addition, increases in NT-proBNP was reported in a few more cases in the bardoxolone than the placebo group (5.2% vs. 1%).

A slight increase in blood pressure was observed in the previous BEACON study when assessed with ambulatory blood pressure monitoring 4 weeks after treatment initiation. Bardoxolone methyl patients had an increase in SBP (mean ± SD) at Week 4 (5.2 ± 10.5 mmHg) compared with a decrease in placebo patients (-2.8 ± 13.5 mmHg). In the Alport studies, blood pressure was however not affected by bardoxolone treatment, but ambulatory blood pressure monitoring was not used.

For oedema peripheral, the overall frequency was slightly higher in bardoxolone than placebo treated subjects (15.6% vs. 12.5%) and there were more cases of higher severity. One severe case and 6 (3.9%) cases of moderate peripheral oedema were reported in bardoxolone treated subjects while 0 moderate and 1 severe case were reported for placebo treated subjects. Most of them resolved with bardoxolone interruption and/or diuretic treatment while some resolved spontaneously without change of treatment. The frequency of mild cases was similar in bardoxolone and placebo treated subjects (9.8% vs. 11.3%). In the pivotal study, 42.9% (vs. 35% in placebo group) and in Analysis Set B, 71 (46.4%) bardoxolone methyl-treated patients shifted into a higher UACR category. One patient randomized to bardoxolone methyl had an SAE of proteinuria.

In Alport syndrome data pool, there were 6 cases of ESRD in bardoxolone treated patients, but one event occurred more than 2 months after study drug discontinuation. The other 5 patients (3.3% in Alport sy analysis set) had initially low indicators of renal function (CKD stage 3 and 4, and A3 stage of albuminuria [UACR ≥300 mg/g]), all received 30mg dose of bardoxolone, and were discontinued from the therapy. In the phase 3 study, a similar number of TEAEs of ESRD was reported in both treatment arms (2 cases in each arm). The other 3 cases of TEAE ESRD in bardoxolone treated patients occurred in the phase 2 study. In the entire study set B, the frequency of the TEAE ESRD was 3.3% (5) and 2.5% (2), respectively, in bardoxolone and placebo treated subjects (see also Exploratory Efficacy Analysis: Kidney Failure Composite Outcome under the efficacy section).

Discontinuation rate due to TEAEs was higher for bardoxolone (22%) than for placebo (5%). The most common TEAEs leading to study drug discontinuation were in the SOC investigations. The most frequently reported TEAE leading to study drug discontinuation for bardoxolone vs. placebo was increased ALT (7.8% vs. 0%).

From previous studies, there is a known risk for elevations of aminotransferases (ALT and AST) and gamma-glutamyltransferase (GGT) during treatment with bardoxolone. This was also noted in the studies performed in Alport syndrome.

Bardoxolone treatment was associated with transient and dose dependent increases in liver enzymes (AST, ALT, GT and to some extent ALP) with a peak at 6 and 8 weeks respectively were reported. TEAEs for increases in ALT and AST occurred in 46.8% and 24.7%, respectively, of patients on bardoxolone treatment. Frequencies in placebo treated subjects were 2.5% and 1.3%, respectively. 5.2% of bardoxolone patients reported GGT increased (1.3% in placebo). According to the laboratory findings, the general effect of bardoxolone however appears to be a slight reduction of the bilirubin concentration however 3.9% (3) bardoxolone treated patients (vs. 0% of placebo treated patients) displayed increased (but none exceeded 2× ULN) bilirubin values. In the entire analysis set B, 7 TEAEs within SOC Hepatobiliary disorders were registered in bardoxolone treated patients (no cases in placebo group) however none of the bardoxolone treated patients had maximum ALT or total bilirubin values that met potential Hy's law criteria.

Bardoxolone treatment was associated with increased ferritin levels that peaked at week 8 after treatment initiation and stayed elevated throughout the study. A higher percentage of bardoxolone methyl-treated patients had one or more on-treatment-high ferritin values compared to placebo-treated patients (21.8% vs 4.9%).

Bardoxolone treated patients displayed a weight decrease that was most pronounced during the first 12 weeks. At week 100, the change was -3.35 vs. 0.16 kg for bardoxolone vs. placebo. Weight loss was more pronounced in patients with high BMI (≥30 kg/m^2) at baseline. The frequency of the TEAE weigh decreased was increased for bardoxolone treated patients (13.0% vs. 1.3%). 7.8% of bardoxolone-treated patients experienced significant weight loss of >7%.

Diarrhoea was reported in a higher frequency in the bardoxolone group compared to placebo (15.6% vs. 7.5% placebo). Within the SOC gastrointestinal disorders in the entire analysis set C (including CKD patients other than Alport), an imbalance in nausea (18.2% vs. 14%) and vomiting (10.7% vs. 7.6%) was also observed in relation to bardoxolone.

Muscle spasms were frequent in both treatment arms, but the frequency was higher for bardoxolone treated subjects (42% vs. 15%). The imbalance was primarily seen in the long term i.e. after more than 12 weeks of treatment. The cases were usually mild, although there were 2 cases of study drug discontinuations.

Hyperkalaemia was reported more frequently for bardoxolone than placebo (14.3% vs. 6.3%). Bardoxolone methyl-treated patients had a slightly more pronounced mean change in potassium from baseline than placebo (0.12±0.430 vs. 0.10±0.481 mEq/L at Week 48).

Upper respiratory tract infections were reported more frequently for bardoxolone than placebo (14.3% and 15.7% vs. 10%). There was also an imbalance in cases of cough (10.4% vs. 3.8%). In the previous BEACON study in patients with stage 4 CKD and T2D, an imbalance for the PT pneumonia was observed (5% vs. 2%). In the Alport patients, only 2 cases of pneumonia were registered (both in the placebo group).

5.5. Uncertainties and limitations about unfavourable effects

The number of patients exposed in the intended population is relatively limited, in particular for adolescents, however there is previous experience of bardoxolone from studies in other indications. In addition, the applicant has proposed a post-marketing registry study. Long-term bardoxolone safety data from the ongoing studies is limited as only 50 Alport syndrome patients that previously received bardoxolone were included in the long-term study. Regarding elderly data, there is insufficient data overall. There is also a lack of clinical experience of bardoxolone use during pregnancy.

The determination process and the rationale for selection of ADRs are not agreed upon. Additional information is requested and the proposed SmPC section 4.8 should be updated accordingly. In addition, a separate table on ADRs in the paediatric population should be considered as a number of common AEs were reported additionally in that population compared to the overall Alport syndrome population.

The previous BEACON study with bardoxolone in patients with T2D and stage 4 CKD was terminated early due to increase in heart failure events. As risk mitigation, patients with uncontrolled diabetes, elevated BNP levels and history of cardiac disease (e.g., cardiac insufficiency NYHA III-IV, LVEF <40%, previous hospitalization for heart failure, symptomatic coronary disease) were excluded in the Alport studies. Alport syndrome generally do not have the severe comorbidities and cardiovascular risks associated with T2DM and Stage 4 CKD. However, if bardoxolone is considered as a lifelong treatment,

the risk factors in the population will likely increase over time, therefore, this particular risk cannot be ruled out in the Alport population.

Given that the more advanced kidney dysfunction in the previous BEACON study may have been one of the factors that contributed to the adverse outcome in the bardoxolone group and patients with CKD stage 4-5 were excluded from the Alport studies as a part of the risk mitigation. With this background, it is noted that the proposed wording of the indication in the present SmPC includes subjects with ERSD. The applicant is therefore requested to justify the use of bardoxolone in subjects with severe renal disease corresponding to CKD 4-5 or to reflect the limitations of the study population in the wording of the indication. Subjects with NYHA III-IV were excluded from the pivotal study to reduce the potential for fluid overload and it is assumed that no patients with NYHA II were included in the study; however, the applicant proposes a contraindication for subjects with NYHA IV only. The applicant should justify the safe use of bardoxolone in subjects with symptomatic heart failure or include these subjects in the contraindication. Considering the increased risk of fluid retention and also the observation of increased BNP in the study in Alport subjects, and that bardoxolone is intended for potential lifelong treatment, it should be discussed how other cardiovascular risk factors should be monitored and handled during treatment. The applicant should also discuss if additional contraindications/precautions should be applied.

The cardiovascular risk of bardoxolone needs further characterisation in the Alport syndrome patients. CV risk has been identified in the early terminated (for harm) BEACON study where fluid retention led to heart failure and excessive number of fatal cases.

The average increase in BNP by bardoxolone is mild, however, the substance appears to cause more pronounced increases in certain individuals. The applicant is requested to investigate whether elevated BNP levels were related to AEs within the cardiac disorders SOC, vascular disorders SOC and cardiac failure SMQ. The applicant is requested to present narratives from the additional cases of peripheral swelling in Alport patients and also present data on BNP/NT-proBNP levels for all cases of peripheral oedema/peripheral swelling. In addition, the applicant is requested to analyse data for risk factors (e.g. baseline CKD stage, use of ACE-Is/ARBs) predisposing to peripheral oedema and rise in BNP.

In the previous BEACON study, a slight increase in blood pressure was observed when assessed with ambulatory blood pressure monitoring. Provided that even small elevations in blood pressure may increase the CV risk if sustained over time, the applicant is requested to discuss the relevance of this finding in relation to the present Alport population. Of note, ambulatory blood pressure monitoring was not used in the Alport studies. In addition, it is not clear whether barodoxolone exhibits acute haemodynamic effects on kidney function, and the relevant discussion is requested.

There are uncertainties regarding the mechanism for the observed ALT and AST elevations. The applicant speculates that the tissue distribution of ALT and AST is broad and that the observed increases in aminotransferases may be due to pharmacological induction of enzymes, also from other sources than the liver. The presented mechanistic support is derived from non-clinical data. However, this is questioned as some patients had high levels of ALT which is more specific for the liver compared to AST and rather points to a liver damage at least in some cases even if no patients randomized to bardoxolone met Hy's law criteria. Therefore, the applicant is requested to discuss any available clinical evidence that support that the observed increases in liver enzymes are derived from other sources than the liver. The applicant is asked to provide details on the 7 TEAEs within SOC Hepatobiliary disorders in order to clarify whether there were other sings of liver injury. The clinical studies in Alport patients included criteria for discontinuing patients with ALT/AST elevations (in total 5 patients were discontinued). These criteria may therefore possibly underestimate the risk for liver injury in the clinical studies compared to clinical use. Drug induced liver injury is therefore proposed as an

important potential risk. Furthermore, monitoring of ALT, AST and bilirubin after the first 12 weeks of treatment should be discussed and recommendations amended to SmPC.

Further discussion on pneumonia is requested given the imbalance in cough and upper respiratory tract infections in the Alport population and given the imbalance in cases of pneumonia observed in previous BEACON study.

Hyperkalaemia was increased in bardoxolone treated patients and the observed cases needs to be further characterised.

The clinical experience of bardoxolone treatment in subjects with Alport syndrome younger than 18 years is very limited. The applicant is asked to discuss the potential impact of bardoxolone on growth and development, including sexual development. Furthermore, according to the PIP, a paediatric study is planned. The applicant is asked to discuss whether the uncertainties regarding safety in adolescents and the planned study should be reflected in the RMP.

The carcinogenic potential of bardoxolone methyl has not been studied in animals. The applicant has provided a carcinogenicity risk assessment based on a weight of evidence approach. There was no imbalance in malignancies in the clinical studies, however given the apparent dual role of Nrf2 in cancer, the applicant is asked to consider including malignancy as a potential risk in the RMP. The applicant is invited to further discuss this.

Furthermore, unless a clear justification can be provided, the testes and epididymides effects observed in the 9-month repeated-dose toxicity in dogs should be included in the SmPC and RMP.

New studies to evaluate the metabolism of bardoxolone methyl are needed to conclude if there are any major and/or active metabolites. Bardoxolone methyl is extensively metabolised, but the metabolism is not sufficiently described. *In vitro* metabolism studies have only been conducted in human microsomes using non-labelled bardoxolone methyl. Extensive metabolism was observed and numerous of metabolites were observed but the majority of the metabolites were not identified. Further investigations *in vitro* for example in hepatocytes or other *in vitro* systems, with bardoxolone methyl, unlabelled or preferably 14C-labelled in an adequate position is requested. In the mass balance and metabolite identification study, the 14C-labelling was in the nitril-moiety which is not an adequate position since the largest metabolite identified in plasma samples is thiocyantate (76%) and the results are not conclusive. The metabolites identified as major metabolites in human plasma require non-clinical qualification. A major objection is raised regarding that the metabolism of bardoxolone methyl needs to be further investigated. Several other concerns have also been raised on the clinical pharmacokinetics, see LoQ.

5.6. Effects Table

Table 51: Effects Table for Imbarkyd for the treatment of chronic kidney disease (CKD) caused by Alport syndrome in adults and adolescents aged 12 years and above

Effect	Short Description	Unit	Bardoxolone	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
LS mean (SE) change from baseline Week 48	ITT population On treatment	mL/ min/ 1.73 m^2	4.71 (1.31)	-4.77 (1.25)	LS Mean Difference (SE) between treatment arms 9.49 (1.81) p<0.0001	402-C-1603/Phase 3

Effect	Short Description	Unit	Bardoxolone	Placebo	Uncertainties/ Strength of evidence	References
LS mean (SE) change from baseline Week 100	ITT population On treatment	mL/ min/ 1.73 m^2	-0.81 (1.56)	-8.45 (1.48)	LS Mean Difference (SE) between treatment arms 7.65 (2.14) P=0.0005	402-C-1603/Phase 3
LS mean (SE) change from baseline Week 52	ITT population Off treatment four weeks	mL/ min/ 1.73 m^2	-0.99 (1.25)	-6.08 (1.24)	LS Mean Difference (SE) between treatment arms 5.09 (1.66) P=0.0021	402-C-1603/Phase 3
LS mean (SE) change from baseline Week 104	ITT population Off treatment four weeks	mL/ min/ 1.73 m^2	-4.52 (1.40)	-8.84 (1.35)	LS Mean Difference (SE) between treatment arms 4.26 (1.88) p=0.0232	402-C-1603/Phase 3
Unfavourable Effects						
Alanine aminotransferase increased	Pooled bardoxolone groups vs placebo	n (%)	36 (46.8%)	1 (1.3%)	Majority of the hepatic TEAEs occurred within the first 12 weeks of treatment.	402-C-1603/Phase 3
Aspartate aminotransferase increased	Pooled bardoxolone groups vs placebo	n (%)	19 (24.7%)	0		402-C-1603/Phase 3
Brain Natriuretic Peptide Increased	Pooled bardoxolone groups vs placebo	n (%)	10 (13.0%)	3 (3.8%)		402-C-1603/Phase 3
Oedema peripheral	Pooled bardoxolone groups vs placebo	n (%)	12 (15.6%)	10 (12.5%)		402-C-1603/Phase 3
Weight decreased	Pooled bardoxolone groups vs placebo	n (%)	10 (13.0%)	1 (1.3%)		402-C-1603/Phase 3
Diarrhoea	Pooled bardoxolone groups vs placebo	n (%)	12 (15.6%)	6 (7.5%)		402-C-1603/Phase 3
UACR shifted into higher category	Pooled bardoxolone groups vs placebo	n (%)	33 (42.9%)	28 (35.0%)		402-C-1603/Phase 3
ESRD	Pooled bardoxolone groups vs placebo	n (%)	2 (2.6%)	2 (2.5%)		402-C-1603/Phase 3
ESRD	Pooled bardoxolone groups vs placebo	n (%)	5 (3.3%)	2 (2.5%)		Analysis set B*

Abbreviations: AE adverse event, ITT Intent to treat population TEAE Treatment emergent adverse event

* Analysis set B consists of the pivotal study (402-C-1603/Phase 3) and data from two additional uncontrolled studies (1603/Phase 2 and 1803).

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

Study 1603/Phase 3 met its prespecified primary and key secondary endpoints, which assessed on-treatment and off-treatment changes in eGFR. The results were supported by the results of Study 1603/Phase 2. The slope of the eGFR curve over time on- and off-treatment however raises some concern.

In the Alport studies, eGFR improved rapidly compared to baseline during the first approximately 12 weeks of bardoxolone treatment. As adequately pointed out by the applicant, clinical conditions or treatment-related increases in eGFR are conventionally thought to be caused by an increase in intraglomerular pressure, which could lead to accelerated damage to the glomeruli and accelerated progression to ESRD. To address this, the applicant has conducted studies to characterise bardoxolone methyl's mechanism for increasing GFR in a non-clinical setting. According to the applicant, these data, together with reports from the scientific literature, indicate that bardoxolone methyl produces acute increases in eGFR by increasing glomerular surface area and by reversing endothelial dysfunction and mesangial cell contraction, thus restoring GFR of individual nephrons without changes in intraglomerular pressure. Clarifying questions on these novel mechanisms are raised**.**

After the initial improvement, eGFR in the bardoxolone arm falls from Week 12 to Week 48 at a rate visually not largely differing from that in the placebo arm in the 1603/Phase 3 study. No effect on the slope of the chronic decrease in eGFR was evident. At withdrawal of treatment at Week 48 eGFR rapidly falls towards baseline. Thus, available data are not indicative of a disease modifying effect. This may indicate that the major benefit with bardoxolone treatment is the rapid pharmacodynamic effects. A discussion regarding clinical relevance of the observed transient (i.e., steep decrease in eGFR after treatment withdrawal) rise in eGFRis requested. A treatment transiently increasing renal function could under some circumstances be beneficial without an accompanying shift in long-term progression rate, in particular in a population with high unmet medical need. Delaying the need of dialysis and/or renal transplantation even with as little as one or two years could be of importance to the patients. At this time point, delaying the need for dialysis and/or transplantation has however not been confirmed in neither of the bardoxolone studies. eGFR for the 19 subjects entering Study 1803 after previous bardoxolone treatment in Study 1603 with three-years-data at data lock point is still over baseline in the feeder study at Week 152 from treatment start. However, patients eligible for inclusion in Study 1803 had no serious AEs during the initial studies and are believed to have a positive benefit-risk for participating in this trial. Patients with a pronounced eGFR decline, reaching ESRD or with nephrotic syndrome were not to be included. The inclusion/exclusion criteria appear to limit the eligible population to the group of previously treated patients who are likely to benefit most from the treatment. As such, any potential future efficacy suggestions derived from this study are severely hampered by the presence of selection bias. In addition, assessment of potential detrimental long-term effects of bardoxolone will be difficult, as Study 1803 is uncontrolled.

Few patients have been exposed to longer treatment periods than two years, and although the slopes appear parallel during the placebo-controlled period, there are scarce data available to exclude more rapid deterioration of GFR over time. Of note, in non-clinical study RTA-P-19006 in mice, there are strong indications of renal toxicity. A question on the kidney findings in the non-clinical setting has

been raised**.** The applicant claims that the toxicity in rodents is caused by a rodent-specific metabolism. The metabolism in humans and potential occurrence of (toxic) metabolites is not fully elucidate. The applicant needs to provide better support/justification for the claim that carboxylic acid metabolites (C17-metabolites) are not generated in humans. In addition, the metabolism of bardoxolone methyl is not sufficiently described and further studies are needed to conclude if there are any major and/or active metabolites. A major objection is raised regarding that the metabolism of bardoxolone methyl needs to be further investigated. In this context, it is also noted that bardoxolone treatment was related to an increase in the urine albumin creatinine ratio (UACR). It is agreed with the applicant that an increase in glomerular filtration could lead to an increase in albuminuria. Notwithstanding, in such case, the excretion of creatinine is expected to raise in parallel. Albumin excretion is a well described surrogate marker for glomerular damage. This needs further discussion. The applicant should present further long-term data as available and discuss the possibility of detrimental long-term effect of treatment. In this context possible rebound effects upon treatment cessation should be discussed. Furthermore, the applicant should discuss whether a direct effect of bardoxolone on the podocytes resulting in an alteration in the filtration barrier can be excluded. The applicant is also asked to discuss whether an increase in UACR has been reported in other products intended for renoprotection. Furthermore, the development of UACR after discontinuation of bardoxolone should also be discussed**.**

The applicant is asked present sensitivity analyses in line with the analyses requested at the fourteenth DMC quarterly data review teleconference on September 1 2020 (i.e., observed eGFR values at each study visit and CFB through the last study visit; observed eGFR using on-treatment data [any data collected after treatment discontinuation is excluded] and their CFB; eGFR using all observed values for patients who discontinued treatment and their CFB).

The proposed indication is broad and includes all stages of renal function in Alport syndrome. It is however questioned that a positive benefit/risk ratio has been shown for the entire target population. No justification has been provided for the safe use in subjects with CKD 4-5 (eGFR <30 mL/min/1.73 m^2), despite this subpopulation being excluded from Study 1603 for safety reasons. Furthermore, medicinal products intended to prevent development/slow progression of chronic renal insufficiency generally tend to be less effective in subjects with severe compared to mild-moderate renal dysfunction due to increasing irreversible damage to the renal parenchyma, e.g., fibrosis and atrophy. In this context, it is noted that subjects with baseline eGFR ≤60 mL/min/1.73 m^2 showed poorer results compared to subjects with baseline eGFR >60 mL/min/1.73 m^2 in the subgroup analysis for the primary analysis at Week 100. Extrapolation of efficacy data from the study population therefore needs to be justified. The applicant is requested to justify the use of bardoxolone in subjects with severe renal disease corresponding to CKD 4-5 (eGFR <30 mL/min/1.73 m^2), taking both safety and efficacy into consideration, or to reflect the limitations of the study population in the wording of the indication.

Concerns are raised regarding study conduct that have the potential of affecting the integrity of the study and validity of the data acquired. The Sponsor unblinded themselves after completion of the first year of treatment despite this being discouraged by the DMC and also made the Year 1 data publicly available without proper communication with the DMC. The Sponsor did not agree to re-consent patients following the publication of Year 1 results. Extensive protocol changes were made well into the duration of the study. Over 50% of the subjects reported at least one major protocol deviation, with over 20% of participants having protocol deviations which included failure of informing PI of weight gain and failure of having an unscheduled assessment and/or increasing BNP or transaminases. This is of concern, as weight increase and elevated liver enzymes are both adverse events of special interest for bardoxolone. Further discussions and clarifications are requested.

The safety profile of bardoxolone methyl seems serious, but manageable. Nevertheless, the caution is needed as safety data assessment is hampered by limited safety data pool in Alport syndrome, and by

limited long-term data available. True long-term bardoxolone safety data are going to remain very limited as only 50 Alport syndrome patients that previously received bardoxolone were included in the long-term study. The number of adolescents included in the clinical development program is limited and precludes firm conclusions on safety profile in that target sub-population. The previous BEACON study with bardoxolone in patients with T2D and stage 4 CKD was terminated early due to increases in heart failure events, possibly related to fluid overload. The observed higher frequency of the TEAE 'BNP increased' and the slight imbalance in the TEAE 'peripheral oedema' in bardoxolone treated patients in the pivotal study is therefore a concern. Further information on these events is requested. The current indication includes patients with NYHA class IV and CKD stage 4 or worse, which is questioned. Considering the increased risk of fluid retention and also the observation of increased BNP in the study in Alport subjects, and that bardoxolone is intended for potential lifelong treatment, it should be discussed how other cardiovascular risk factors should be monitored and handled during treatment. The applicant should also discuss if additional contraindications/precautions should be applied.

From previous studies, there is a known risk for elevations of aminotransferases (ALT and AST) and GGT during treatment with bardoxolone. This was also noted in the pivotal study in patients with Alport syndrome. According to the applicant, the increases in aminotransferases may be due to pharmacological induction of enzymes, also from other sources than the liver, and not related to mechanisms involved in liver injury. Although no patients randomized to bardoxolone met Hy's law criteria, this is questioned and needs to be further substantiated. In addition, monitoring of ALT, AST and bilirubin after the first 12 weeks of treatment should be discussed.

Not negligible portion of Alport syndrome patients had bardoxolone discontinuation or interruption due to AEs. Besides renal function monitoring, there is a need for monitoring hepatic function, body weight, serum potassium (not presently agreed with the applicant), and for signs and symptoms of heart failure.

5.7.2. Balance of benefits and risks

Study 1603/Phase 3 met its primary and secondary endpoints. However, available data are not indicative of a disease modifying effect. The major benefit with bardoxolone treatment may instead be the rapid pharmacodynamic effects which, if caused by an increase in intraglomerular pressure, could lead to accelerated damage to the glomeruli and accelerated progression to ESRD. The possibility of detrimental long-term effect of bardoxolone treatment and possible rebound effects upon treatment cessation needs further discussion. Furthermore, the proposed indication is broad and includes all stages of renal function in Alport syndrome. It is questioned that a positive benefit/risk ratio has been shown for the entire target population.

Concerns regarding integrity of study conduct and validity of acquired data need to be addressed.

The potential risk of fluid retention, an increased cardiac volume load and, in a longer term, development of heart failure is not considered sufficiently addressed.

Increases in BNP and increases in aminotransferases (ALT, AST) were common TEAEs during bardoxolone treatment. Furthermore, bardoxolone treatment was related to an increase in the urine albumin creatinine ratio.

Considering all favourable and unfavourable effects, the benefit-risk balance is currently negative.

5.7.3. Additional considerations on the benefit-risk balance

Study 1603/Phase 3 included 12 subjects aged 12-<18 years in the placebo arm and 11 subjects in the bardoxolone arm.

The clinical experience of bardoxolone treatment in subjects with Alport syndrome younger than 18 years is very limited. The applicant is asked to discuss the potential impact of bardoxolone on growth and development, including sexual development. Furthermore, according to the PIP, a paediatric study is planned. The applicant is asked to discuss whether the uncertainties regarding safety in adolescents and the planned study should be reflected in the RMP.

The paediatric population in Study 1603/Phase 3 had a mean baseline eGFR values of approximately 70 mL/min/1.73 m^2. The paediatric subpopulation had the largest annual rates of eGFR decline prior to study entry (-11 mL/min/1.73 m^2 per year). Treatment with bardoxolone methyl resulted in a decrease from baseline in eGFR of 1.4 mL/min/1.73 m^2 at Week 100, while treatment with placebo resulted in a decrease in eGFR of -15 mL/min/1.73 m^2. At Week 104, following a 4-week off-treatment period, mean changes from baseline in eGFR -2.9 mL/min/1.73 m^2 for bardoxolone methyl-treated paediatric patients and -18 mL/min/1.73 m^2 for placebo-treated paediatric patients. In summary, there was no indication of a poorer response to bardoxolone in the limited paediatric efficacy population.

The popPK analysis results show that age is not a statistically significant predictor for bardoxolone pharmacokinetics. However, further detail of exposure vs body weight in support of the dosing recommendation for adolescents as well as a discussion of a potential weight restriction, knowing that no information on bardoxolone PK in subjects below 46 kg is available, is requested.

5.8. Conclusions

The overall benefit/risk balance of Imbarkyd is currently negative.