
Clinical Study Protocol

Study Intervention	Balcinrenone/dapagliflozin
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MIRO-CKD:

A Phase IIb, Multicentre, Randomised, Double-Blind, Dose-finding Study to Evaluate the Efficacy, Safety and Tolerability of Balcinrenone in Combination with Dapagliflozin Compared with Dapagliflozin in Patients with Chronic Kidney Disease and Albuminuria

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This protocol has been subject to a peer review according to AstraZeneca Standard procedures. The protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Standard - Bioethics and in compliance with prevailing laws and regulations.

Version Scope: Global

Brief Title: A Phase IIb Dose-Finding Study of Balcinrenone/Dapagliflozin in Patients with CKD and Albuminuria

Study Phase: Phase IIb

Acronym: MIRO-CKD

AstraZeneca Study Clinical Lead Name and Contact Information will be provided separately.

Study Clinical Lead is responsible for the clinical integrity of the study (for example, the study physician or scientist).

SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	Date
CSP v2.0	02-Oct-2024
CSP v.1.0 (Original Protocol)	11-Jan-2024

CSP Version 2.0 02-OCT-2024

This modification is considered to be non-substantial based on the criteria set forth in Regulation (EU) No 536/2014 of the European Parliament because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Modification:

The Clinical Study Protocol version 1.0, dated 11 January 2024, was modified to add changes related to DMC composition and clarify EU-CTR SUSAR reporting. Additional minor updates and formatting edits were also implemented throughout for clarification and consistency.

Summary of Changes:

List of Non-Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
List of Abbreviations	Abbreviations list updated	Missing abbreviations added
Section 1.1 Synopsis	DMC composition updated CCI [REDACTED]	Updated in line with local CSP for EU/EEA
Section 1.1 Synopsis	Statistical Methods wording updated	Updated to align with DMC charter
Section 1.3 Schedule of Activities	Added footnote for optional assessments	Footnote added for clarification
Section 2.3.1 Risk Assessment (Table 2)	Updates to Renal events/AKI, Hypotension and Diabetic ketoacidosis in patients with diabetes mellitus	Updated to align with new IB language
Section 5.2 Exclusion Criteria	Criterion 3 wording updated	Rephrased to clarify that 'myocardial infarction' as well as

		'unstable angina' are considered 'acute coronary syndrome'
Section 5.2 Exclusion Criteria	Criterion 4 wording updated	Rephrased to emphasise all ANCA vasculitis and lupus nephritis are excluded
Section 6.4 Blinding	DMC composition updated CCI [REDACTED]	Updated in line with local CSP for EU/EEA
Section 8.2.1 Primary Variable: Urinary Albumin-to-Creatinine Ratio	Urine sample collection for UACR calculation wording updated	To keep consistent with footnote 'f' on Table 1 'Schedule of Activities'.
Section 8.4.4 Adverse Events of Special Interest	Added text stating that predefined PTs are used, including a reference to the new Appendix G	Added for clarification and to align with SAP
Section 9.4.3.1 Adverse Events of Special Interest	Added reference to the new Appendix G	Added for clarification and to align with SAP
Section 9.5 Interim Analysis	Statistical Methods wording updated	Updated to align with DMC charter
Section 9.6 Data Monitoring Committee	DMC composition updated CCI [REDACTED]	Updated in line with local CSP for EU/EEA.
Appendix A1 Regulatory and Ethical Considerations	Regulatory Reporting Requirements for SAEs updated	Added text to clarify EU-CTR reporting for SUSARs into EudraVigilance
Appendix A5 Committees Structure Data Monitoring Committee	DMC composition updated CCI [REDACTED]	Updated in line with local CSP for EU/EEA
Appendix B1 Definition of AEs	Definition of AEs updated	Definition of AEs Updated based on current CSP template
Appendix D6 Laboratory Tests	HSV infection testing updated	Updated due to changes in diagnostic tests available for HSV infection testing
Appendix D7 References	Added References to Appendix D	Missing reference added

Appendix E Country Specific Requirements	Country-specific requirement of pregnancy testing during each visit added for Austria	Update made to comply with local EU country requirement.
Appendix F Strong and Moderate Cytochrome P450 3A4 (CYP3A4) Inhibitors and Inducers	Additional information on route of administration of CYP450 inhibitors/inducers included.	Clarification included to allow for the use of non-systemically administered moderate/strong CYP450 inhibitors/inducer drugs.
Appendix G List of PTs Defining the Adverse Events of Special Interest	List of PTs Defining the Adverse Events of Special Interest added	Added for clarification and to align with SAP

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
AKI	Acute kidney injury
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/transaminase
AST	Aspartate aminotransferase/transaminase
AUC	Area under the curve
AxMP	Auxilliary medicinal product
BP	Blood pressure
CI	Confidence interval
CKD	Chronic kidney disease
CMV	Cytomegalovirus
COVID-19	Coronavirus 2019
CRO	Contract Research Organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Clinical Trial
CTIS	Clinical Trial Information System
CV	Cardiovascular
CYP	Cytochrome P450
DAE	Discontinuation due to Adverse Event (Premature discontinuation of treatment with investigational product due to an adverse event)
DBP	Diastolic blood pressure
DES	Data Entry Site
DILI	Drug-induced liver injury
DKA	Diabetic ketoacidosis
DKD	Diabetic kidney disease
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DUS	Disease under study
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

Abbreviation or special term	Explanation
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	End of treatment
EOTV	End of treatment visit
ESKD	End stage kidney disease
EU	European union
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GFR	Glomerular filtration rate
GM	Geometric mean
HbA1c	Glycated haemoglobin
HBS	Human Biological Sample(s)
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HBc	Hepatitis B core
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HF	Heart failure
hHF	Hospitalisation for heart failure
HR	Hazard ratio
HSV	Herpes simplex virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
INR	International normalised ratio

Abbreviation or special term	Explanation
IQRMP	Integrated Quality Risk Management Plan
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous
K ⁺	Potassium
LDH	Lactate dehydrogenase
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MR	Mineralocorticoid receptor
MRA	Mineralocorticoid receptor antagonist
NIMP	Non-investigational Medicinal Product
PI	Principal investigator
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred term
PTDV	Premature Treatment Discontinuation Visit
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTL	Quality tolerance limits
QTcF	QT interval corrected for heart rate using Fridericia's correction
RAAS	Renin–angiotensin–aldosterone system
RNA	Ribonucleic acid
RT-PCR	Real-time reverse-transcription polymerase chain reaction
RTSM	Randomisation and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus disease 2
SBP	Systolic blood pressure
SGLT1	Sodium-glucose cotransporter-1
SGLT2	Sodium-glucose cotransporter-2
SMQ	Standardised MedDRA Query
SoA	Schedule of Activities
SoC	Standard of cCre
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

Abbreviation or special term	Explanation
TBL	Total bilirubin
UACR	Urinary albumin-to-creatinine ratio
ULN	Upper limit of normal
CCI	
wks	Weeks
WMA	World Medical Association
WOCBP	Woman of childbearing potential

1 **PROTOCOL SUMMARY**

1.1 **Synopsis**

Protocol Title:

A Phase IIb, Multicentre, Randomised, Double-Blind, Dose-Finding Study to Evaluate the Efficacy, Safety and Tolerability of Balcinrenone in Combination with Dapagliflozin Compared with Dapagliflozin in Patients with Chronic Kidney Disease and Albuminuria.

Brief Title:

A Phase IIb Dose-Finding Study of Balcinrenone/Dapagliflozin in Patients with CKD and Albuminuria.

Regulatory Agency Identifier Number(s):

IND Number: 167463

EU CT number: 2023-509709-63

Rationale:

Mineralocorticoid receptor antagonists (MRA) have been shown to reduce chronic kidney disease (CKD) progression in patients with diabetic kidney disease while sodium-glucose cotransporter-2 (SGLT2) inhibitors have demonstrated a similar benefit in patients with CKD, both with or without type 2 diabetes mellitus (T2DM).

The MRA finerenone has demonstrated benefits on the composite endpoint of sustained decline in estimated glomerular filtration rate (eGFR), kidney failure, and renal death (FIDELIO-DKD study), and the composite of cardiovascular (CV) death, myocardial infarction, stroke, and hospitalisation for heart failure (FIGARO-DKD study) in patients with CKD and T2DM; however, the risk of hyperkalaemia remains.

Balcinrenone is a novel selective mineralocorticoid receptor (MR) modulator that exhibits a differentiated mode of action when compared to approved MRAs. This differentiated mode of action is expected to maintain the treatment benefits while reducing the risk of hyperkalaemia, when compared to approved MRAs.

Dapagliflozin, an SGLT2 inhibitor, reduced the risk of sustained decline in eGFR, end-stage kidney disease (ESKD), or death from renal or CV causes in patients with CKD both with and without T2DM in the DAPA-CKD study.

The mechanisms of action for balcinrenone and dapagliflozin are different and likely complementary, and therefore expected to have additive treatment benefits.

This is a dose-finding study aiming to identify an optimal dose of balcinrenone in combination with dapagliflozin for a future Phase III study in patients with CKD. This study will evaluate the effect of the balcinrenone/dapagliflozin combination on urinary albumin-to-creatinine ratio (UACR), compared with dapagliflozin in patients with CKD. The study will also evaluate tolerability and general safety of balcinrenone/dapagliflozin.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To determine whether balcinrenone/dapagliflozin is superior to dapagliflozin in reducing albuminuria	Relative change in UACR from baseline to Week 12
Safety	
To evaluate the safety and tolerability of balcinrenone/dapagliflozin compared with dapagliflozin	• Occurrence and time to first occurrence of AE, SAE, SAE with outcome death, AE leading to discontinuation of IMP and possibly related AE as assessed by the investigator • Observed laboratory values and changes from baseline • Observed vital sign values (including BP and pulse rate) and changes from baseline • Observed ECG parameters and changes from baseline • Occurrence and time to first event of AESI (hyperkalaemia, renal events/AKI, and hypotension)

AE = Adverse event; AKI = Acute kidney injury; ECG = Electrocardiogram; IMP = Investigational medicinal product; SAE = Serious adverse event; UACR = Urinary albumin-to-creatinine ratio.

For exploratory objectives and endpoints, see Section 3 of the protocol.

Overall Design Synopsis:

- This is a Phase IIb, multicentre, randomised, double-blind, dose-finding, parallel group, double-dummy study aiming to determine the effect on albuminuria, as well as safety and tolerability, of balcinrenone/dapagliflozin compared with dapagliflozin, when given once daily on top of other Standard of Care (SoC) to patients with CKD and albuminuria.
- Study population will include participants with CKD (eGFR ≥ 25 to < 60 mL/min/1.73 m²) and UACR > 100 mg/g to ≤ 5000 mg/g. Participants with or without a diagnosis of T2DM and with or without an SGLT2 inhibitor treatment at screening are eligible for the study.
- After screening and initial confirmation of eligibility, participants will be randomised in a 1:1:1 ratio to receive either balcinrenone/dapagliflozin 15 mg/10 mg,

balcinrenone/dapagliflozin 40 mg/10 mg, or dapagliflozin 10 mg. The randomisation will be stratified by eGFR at screening (≥ 25 to < 45 mL/min/1.73 m² and ≥ 45 to < 60 mL/min/1.73 m²), SGLT2 inhibitor treatment at screening (yes/no), and T2DM status at screening (yes/no).

- The study will be conducted at approximately 110 sites in approximately 16 countries globally.

Disclosure Statement:

This is a parallel group treatment study with 3 arms that is participant-, investigator-, and sponsor-blinded.

Number of Participants:

At least 300 participants will be randomised in order to have 300 evaluable participants.

Study Arms and Duration:

Participants will be randomised to one of 3 treatment arms in a 1:1:1 ratio:

- Balcinrenone/dapagliflozin 15 mg/10 mg
- Balcinrenone/dapagliflozin 40 mg/10 mg
- Dapagliflozin 10 mg

For each participant, the total duration of participation will be approximately 23 weeks: an up to 3-week screening period followed by a 12-week treatment period, and a 8-week follow-up period after end of investigational medicinal product (IMP) treatment.

Data Monitoring/Other Committee: Yes

A Data Monitoring Committee (DMC) consisting of AstraZeneca representatives (who are neither involved in the study conduct nor in the balcinrenone/dapagliflozin programme) CCI

CCI

Statistical Methods:

The primary efficacy hypothesis of the study is that in adults with CKD and albuminuria, balcinrenone/dapagliflozin (either 40 mg/10 mg or both 40 mg/10 mg and 15 mg/10 mg, once daily) is superior to dapagliflozin 10 mg in reducing albuminuria, as assessed by the relative change in UACR from baseline to Week 12.

The primary objective will be addressed by an estimand which assesses the differences in outcomes in treatment groups over the period from randomisation until Week 12, to reflect the

effect of the initially assigned randomised IMP, irrespective of concomitant treatment, or discontinuation of IMP, and in the absence of death, initiation of dialysis or kidney transplant, withdrawal of consent, and lost to follow-up.

Baseline for UACR will be defined as the geometric mean of 3 UACR values derived from first morning void samples collected at 3 consecutive days, the third being the randomisation date (prior to the first dose of IMP).

The change from baseline in log-transformed UACR at Week 12 for each of the 2 doses of balcinrenone combined with dapagliflozin 10 mg and dapagliflozin 10 mg will be estimated in a mixed model for repeated measures. The estimated change from baseline for each treatment arm, as well as the difference between the 2 dose arms and the dapagliflozin 10 mg arm, will be back-transformed onto the original scale to give relative changes from baseline and the relative difference between treatments.

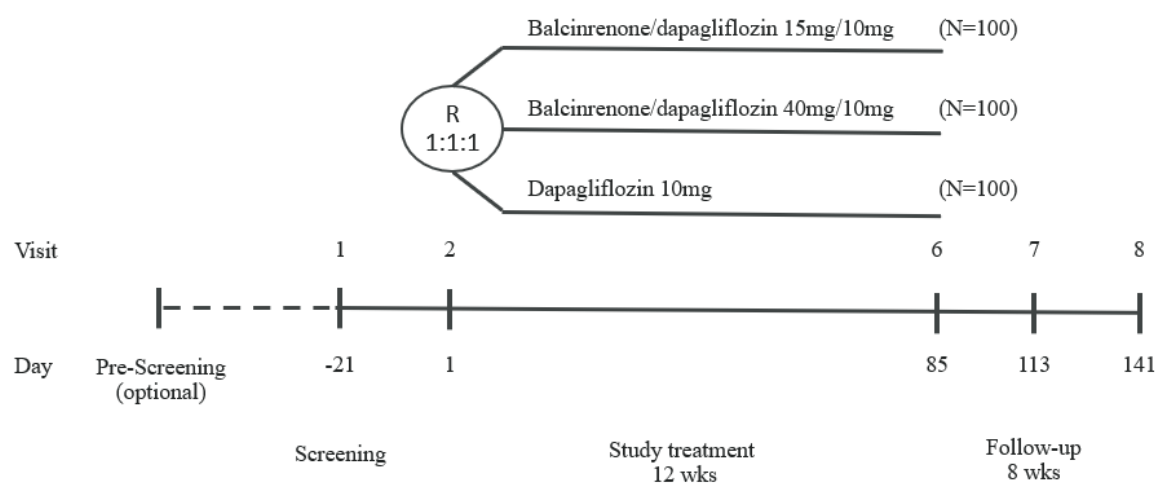
Each balcinrenone/dapagliflozin arm will be compared to the dapagliflozin arm CCI at a CCI significance level of CCI the high-dose arm will be tested against the comparator, and CCI the low-dose arm will be tested against the comparator at the CCI. The full analysis set (FAS) will be used for the primary efficacy analysis. Sensitivity analyses will be described in the statistical analysis plan (SAP).

Safety and tolerability will be evaluated in terms of adverse events (AE), clinical laboratory variables, vital signs, and electrocardiogram (ECG). In addition, extra evaluation will be done for the following adverse events of special interest (AESI): hyperkalaemia, hypotension, and renal events/acute kidney injury (AKI). Exposure to IMP will be described. Safety analyses will be performed on the FAS.

CCI are planned, with the purpose to CCI for CCI outside of this study.

1.2 Schema

Figure 1 Study Design



1.3 Schedule of Activities

Table 1 Schedule of Activities

Procedure	Pre-screening	Screening/ Enrolment	Baseline/ Randomisation	Intervention Period (12 Weeks)			EOTV/ PTDV	Safety/ CCI Follow-up 1	CCI Follow-up 2	Details in CSP Section or Appendix
Visit	Optional	1	2	3	4	5	6	7	8	
Day (± days)		-21 to -1	1	8 ± 2	29 ± 3	57 ± 3	85 ± 3/ NA	113 ± 4	141 ± 4	
Informed consent (abbreviated)	X									Section 5.1 and Appendix A 3
Creatinine and/or eGFR, blood sample (local laboratory)	X ^a									Section 8.3.5
UACR, spot urine test (local laboratory)	X ^a									Section 8.3.5
Informed consent (full)		X								Section 5.1 and Appendix A 3
Inclusion and exclusion criteria		X	X							Section 5.1 and Section 5.2
Enrolment in IRT/RTSM		X								Section 6.3
Randomisation in IRT/RTSM			X							Section 6.3
Demography		X								Section 5.1
Physical examination		X	X				X			Section 8.3.1
Body weight and height ^b		X					X			Section 8.3.2
Medical/surgical history		X	X							Section 5.1

Table 1 **Schedule of Activities**

Procedure	Pre-screening	Screening/ Enrolment	Baseline/ Randomisation	Intervention Period (12 Weeks)			EOTV/ PTDV	Safety/ CCI Follow-up 1	CCI Follow-up 2	Details in CSP Section or Appendix
Visit	Optional	1	2	3	4	5	6	7	8	
Day (± days)		-21 to -1	1	8 ± 2	29 ± 3	57 ± 3	85 ± 3/ NA	113 ± 4	141 ± 4	
Concomitant medications		X	X	X	X	X	X	X	X	Section 6.9
Pregnancy test (WOCBP only) ^c		X	X				X			Section 8.3.5
FSH (amenorrhoeic women < 50 years old only)		X								Section 8.3.5
Vital signs		X	X	X	X	X	X	X	X	Section 8.3.3
12-lead ECG		X	X				X	X		Section 8.3.4
Safety panel, blood sample (central laboratory)		X	X	X ^d	X	X	X	X	X ^e	Section 8.3.5
Potassium and eGFR, blood sample (local laboratory)				X						Section 8.3.5
Safety panel, urine sample (central laboratory)		X	X		X	X	X	X		Section 8.3.5
UACR, urine sample, (central laboratory) ^f		X	X		X	X	X			Section 8.3.5

Table 1 Schedule of Activities

Procedure	Pre-screening	Screening/ Enrolment	Baseline/ Randomisation	Intervention Period (12 Weeks)			EOTV/ PTDV	Safety/ CCI Follow-up 1	CCI Follow-up 2	Details in CSP Section or Appendix
Visit	Optional	1	2	3	4	5	6	7	8	
Day (± days)		-21 to -1	1	8 ± 2	29 ± 3	57 ± 3	85 ± 3/ NA	113 ± 4	141 ± 4	
PK sampling balciarenone and dapagliflozin (central laboratory)				X (pred ose)	X (pred ose)		X ^e			Section 8.5
Olink biomarker panel, blood sample (central laboratory)			X		X		X ^e			Section 8.8
IMP dispensation			X		X	X				Section 6.1
IMP collection and accountability					X	X	X			Section 6.5
IMP compliance reminder				X	X	X	X			Section 6.5
Adverse events ^h	X (SAE only)	X (SAE only)	X	X	X	X	X	X	X	Section 8.4 and Appendix B

^a Blood sample for creatinine and/or eGFR measurement(s) and urine sample (spot urine test) for UACR assessment.

^b Height measurement will be performed at Visit 1 only.

^c Serum test at screening/enrolment (for determination of eligibility), urine test at randomisation/pre-dose and EOTV/PTDV. Adhoc test to be used at the discretion of investigators during the treatment period in case of suspected pregnancy. If required by local authorities, additional pregnancy test can be done during the study and urine pregnancy test can be replaced by a local laboratory blood pregnancy test.

^d Only serum Na⁺, serum K⁺, blood urea nitrogen, serum creatinine, and eGFR will be assessed.

^e Only serum CCI and CCI will be assessed.

^f Urine samples for UACR assessment should be collected by the participant from first morning urine voidings, except for Visit 1 (screening/enrolment), where the urine samples (spot urine test) will be collected during the clinic visit. Before Visit 2 (baseline/randomisation), Visit 4, Visit 5 and Visit 6 (EOTV) the participant should collect 3 first morning urine void specimens preferably on 3 consecutive days (see Section 8.2.1).

- ^g PK sample and blood sample (plasma) for Olink biomarker panel only applicable for EOTV, not PTDV. Visit and sampling at EOTV will take place one day after last dose.
- ^h SAEs will be collected from Visit 1 (signing full informed consent) and AEs from baseline/randomisation. AEs and SAEs will be collected throughout the study intervention period and the safety follow-up period. Only SAEs related to the study procedures will be collected during optional pre-screening visit (Section 8.4.8).

Assessments highlighted in grey are optional

2 INTRODUCTION

2.1 Study Rationale

MRAs and SGLT2 inhibitors have separately demonstrated reduction of the risk of CKD progression and the risk of CV death via independent mechanisms. The combined usage of MRAs with SGLT2 inhibitors is therefore expected to provide complementary and additive treatment benefits.

The MRA finerenone has demonstrated benefits on the composite endpoint of sustained decline in eGFR, kidney failure, and renal death (FIDELIO-DKD study), and the composite of CV death, myocardial infarction, stroke, and hHF (FIGARO-DKD study) in patients with CKD and T2DM; however, the risk of hyperkalaemia remains ([Bakris et al 2020](#), [Pitt et al 2021](#)). Dapagliflozin, an SGLT2 inhibitor, reduced the risk of sustained decline in eGFR, ESKD, death from renal or CV causes in patients with CKD both with and without T2DM in the DAPA-CKD study ([Heerspink et al 2020](#)).

Balcinrenone (previously known as AZD9977) is a novel selective MR modulator with a differentiated mode of action when compared to approved MRAs, which predicts a reduced risk of hyperkalaemia.

The mechanism of action for balcinrenone and dapagliflozin are different and likely complementary. The treatment effects of balcinrenone and dapagliflozin on kidney outcomes are expected to be additive given that the main biological effects of balcinrenone would be to block MR-driven oxidative stress, inflammation, and fibrosis, and for dapagliflozin to reduce intraglomerular pressure and combined with osmotic diuresis to reduce volume overload, BP, and lower preload and afterload, which may both preserve kidney function and improve CV function. For detailed information see the balcinrenone IB and the dapagliflozin IB.

This is a dose-finding study aiming to identify an optimal dose of balcinrenone in combination with dapagliflozin for a future Phase III study in patients with CKD. This study will evaluate the effect of the balcinrenone/dapagliflozin combination on UACR, compared with dapagliflozin in patients with CKD. The study will also evaluate tolerability and general safety of balcinrenone/dapagliflozin.

2.2 Background

Approximately 10% of adults worldwide are affected by CKD ([Bikbov et al 2020](#), [Xie et al 2018](#)). CKD is a serious progressive condition defined by decreased kidney function (shown by reduced eGFR), or markers of kidney damage (eg, albuminuria) or both, for at least 3 months. CKD is associated with increased risk of ESKD, HF ([He et al 2017](#)), CV, and all-cause death ([Jankowski et al 2021](#), [Webster et al 2017](#), [Bikbov et al 2020](#)). There is a

growing unmet medical need for treatments that can reduce the global burden of CKD.

Dapagliflozin is a highly selective and reversible inhibitor of SGLT2, the major transporter responsible for glucose reabsorption in the kidney. In the DAPA-CKD study ([Heerspink et al 2020](#)), dapagliflozin administered on top of SoC demonstrated significant clinical benefit in patients with a diagnosis of CKD and UACR ≥ 200 mg/g, both with and without T2DM. In this study, dapagliflozin reduced the risk of the primary composite endpoint of progression to ESKD, sustained $\geq 50\%$ decline in eGFR or CV/renal death compared to placebo (HR 0.61, 95% CI, 0.51 to 0.72; $P < 0.001$), the risk of hHF/CV death (HR 0.71, 95% CI, 0.55 to 0.92; $P = 0.009$), and all cause mortality (HR 0.69; 95% CI, 0.53 to 0.88; $P = 0.004$). Despite the significant benefit demonstrated by SGLT2 inhibitors on top of RAAS inhibitors, an unmet need remains in this population (in DAPA-CKD study, the primary endpoint occurred at a rate of 4.6 events/100 patient-years in patients randomised to dapagliflozin added to SoC).

Balcinrenone is a novel selective MR modulator with a differentiated mode of action versus traditional MRAs. Preclinical data have demonstrated separation of beneficial organ-protective effects from the electrolyte effects typical for the MRA class. This mechanism-based differentiation has the potential to translate into a reduced risk of hyperkalaemia in clinical use. Phase I studies have demonstrated balcinrenone's MR-modifying effects in healthy subjects and in patients with HF and CKD, and indicated that it was well tolerated, with no safety concerns raised ([Bamberg et al 2018](#)). The small Phase IIb study MIRACLE (D6402C00001) showed that all balcinrenone/dapagliflozin doses used in the study (15, 50, or 150 mg in combination with dapagliflozin 10 mg) showed numerically beneficial effects on UACR and other efficacy markers compared to dapagliflozin alone and the safety profile did not raise any concerns. For details, refer to the IB for balcinrenone.

The combination of SGLT2 inhibitors and MRAs has demonstrated additive efficacy on reducing UACR ([Provenzano et al 2022a](#)) and a subanalysis of patients in the FIDELIO and FIGARO studies supports cardio-renal benefits from finerenone treatment also in patients already taking SGLT2 inhibitors ([Rossing et al 2022](#)). Moreover, combining MRA with SGLT2 inhibitor appears to reduce the risk of hyperkalaemia; fewer events of moderate/severe hyperkalaemia were seen in HF patients on MRA in the dapagliflozin arm compared to the placebo arm in the DAPA-HF study ([Shen et al 2021](#)). In the FIDELIO pooled analysis, a lower incidence of hyperkalaemia was reported with concomitant treatment of SGLT2 inhibitors and finerenone than with finerenone alone ([Rossing et al 2022](#)).

2.3 Benefit/Risk Assessment

Dapagliflozin has a well-established safety profile and has global market approvals for use in HF, CKD, and T2DM. Balcinrenone is a new molecular entity in clinical development with

more limited experience in healthy volunteers and patients with HF and impaired kidney function. More detailed information about the known and expected benefits and risks of balcinrenone and dapagliflozin can be found in the respective IBs.

2.3.1 Risk Assessment

All protocol-related procedures, including blood and urine sampling, vital signs measurements, and 12-lead ECGs are established routine assessments in the management of patients with CKD, ie, no added risk compared to routine care. Potential risks related to the IMPs are summarised in [Table 2](#).

Table 2 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Balcinrenone/dapagliflozin		
Hyperkalaemia	Hyperkalaemia is a well-known adverse effect of MRAs, although balcinrenone exhibits a differentiated mode of action that is expected to reduce the risk of hyperkalaemia, according to nonclinical data. The dapagliflozin component is expected to further reduce the risk of hyperkalaemia as dapagliflozin reduces the risk for moderate/severe hyperkalaemia in patients taking MRAs (Shen et al 2021). No safety concerns have been raised with regards to serum K⁺ observed in Phase I studies with balcinrenone, including studies in healthy subjects and in patients with HF and eGFR in the range of 40 to 70 mL/min/1.73 m². In the Phase IIb MIRACLE (D6402C00001) study, which compared balcinrenone/dapagliflozin to dapagliflozin alone in patients with HF and eGFR in the range of 30 to 60 mL/min/1.73 m², a comparable number of patients with serum K⁺ > 5.5 mmol/L were seen in the dapagliflozin 10 mg active control arm and in the balcinrenone/dapagliflozin 15 mg/10 mg and 50 mg/10 mg treatment arms, with a tendency toward higher numbers in the balcinrenone/dapagliflozin 150 mg/10 mg treatment arm. Furthermore, mean serum K⁺ levels were comparable between the dapagliflozin 10 mg active control and the balcinrenone/dapagliflozin 15 mg/10 mg arms throughout the 12-week intervention, but tended to	This is a pre-specified AESI in the study. Serum K⁺ level ≥ 3.5 and ≤ 5.0 mmol/L is an inclusion criterion (see inclusion criterion 4). Serum K⁺ will be monitored at all scheduled visits and at unscheduled visits if needed as per investigator's judgment. See also Sections 5.3.2 and 7.1.1. Specific discontinuation criteria for hyperkalaemia are provided. Participants will be instructed to contact the trial site in case of acute illness that could increase the risk of hyperkalaemia or acute kidney injury, see Section 5.3.2.

Table 2 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	be higher in the balcinrenone/dapagliflozin 50 mg/10 mg and 150 mg/10 mg treatment arms.	
Renal events/AKI	Both SGLT2 inhibitor and MRA medications cause a transient reduction in eGFR that in itself is not a safety concern, but represents a pharmacological effect on glomerular haemodynamic (Adamson et al 2022, Rossignol et al 2014). Preclinical studies suggest that this reduction in GFR may actually contribute to the reno-protective effects of these agents and to their effect in slowing down CKD progression (Agarwal et al 2022, Provenzano et al 2022b). Nevertheless, it is reasonable to monitor kidney function after initiation of an MR modulator and an SGLT2 inhibitor in higher risk patients, including those with advanced CKD. Traditionally, an eGFR decrease by up to 30% from baseline is considered acceptable (Yau et al 2022), and current guidelines recommend a further evaluation in case of an eGFR dip of > 30% in subsequent tests, thus exceeding expected variability (KDIGO-CKD 2023). No safety concerns have been raised with regards to kidney function observed in Phase I studies with balcinrenone, including studies in healthy subjects and in patients with HF and eGFR in the range of 40 to 70 mL/min/1.73 m². In the Phase IIb MIRACLE (D6402C00001) study, which compared balcinrenone/dapagliflozin to dapagliflozin alone in patients with HF and eGFR in the range of 30 to 60 mL/min/1.73 m², there were few reported AEs related to renal function with a balanced distribution across the treatment arms. There were generally small mean decreases in eGFR from baseline in all treatment arms, that did not raise any safety concerns.	This is a pre-specified AESI in the study. Serum creatinine/eGFR will be monitored at all visits. Specific discontinuation criteria for the management of initial eGFR decrease are provided. Participants will be instructed to contact the trial site in case of acute illness that could increase the risk of hyperkalaemia or acute kidney injury, see Section 5.3.2.
Hypotension	Both SGLT2 inhibitor and MRA medications are associated with a BP lowering effect. No safety concerns have been raised with regards to BP observed in Phase I studies with balcinrenone, including studies in healthy participants and in patients with HF and eGFR in the range of 40 to 70 mL/min/1.73 m².	This is a pre-specified AESI in the study. Systolic BP < 100 mmHg is an exclusion criterion (exclusion criterion 2). BP will be monitored at all visits.

Table 2 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	In the Phase IIb MIRACLE (D6402C00001) study, which compared balcinrenone/dapagliflozin to dapagliflozin alone in patients with HF and eGFR in the range of 30 to 60 mL/min/1.73 m ² , there were small reductions in systolic and diastolic BP in all combination arms compared to dapagliflozin alone, that did not raise any safety concerns. Two patients reported predefined AEs related to hypotension in the balcinrenone/dapagliflozin 150/10 mg arm, 1 with PT hypotension and 1 with PT syncope, (both non-serious), versus none in the other arms.	
Diabetic ketoacidosis in patients with diabetes mellitus	DKA has been identified as an important identified risk for dapagliflozin in patients with diabetes. DKA was commonly seen in T1DM patients treated with dapagliflozin but was rare in clinical trials with T2DM patients. For more details regarding the frequency of this risk see section 5.6 of the dapagliflozin IB.	T1DM patients are excluded from the study (see exclusion criterion 8). Specific discontinuation criteria for DKA are provided.

2.3.2 Benefit Assessment

All participants randomised in the study will receive dapagliflozin treatment and may also benefit from frequent health check-ups.

Data from the DAPA-CKD study show short-term beneficial effects of dapagliflozin on decreasing UACR, as well as long term superiority to placebo in reducing the incidence of the primary composite endpoint of $\geq 50\%$ sustained decline in eGFR, reaching ESKD, CV or renal death when added to current background therapy ([Jongs et al 2021](#), [Heerspink et al 2020](#)).

Additionally, the participants in the arms that also receive balcinrenone in combination with dapagliflozin are expected to have increased benefit compared with dapagliflozin:

- Data from patients with DKD show clinical benefit of MRAs in preventing the progression to end-stage kidney disease ([Bakris et al 2020](#)); the limited data available in patients with non-diabetic CKD suggest that MRAs also have a positive effect in this type of renal patients ([Provenzano et al 2022b](#)).

- The Phase IIb MIRACLE (D6402C00001) study which compared balcinrenone/dapagliflozin to dapagliflozin in patients with HF and eGFR in the range of 30-60 mL/min/1.73 m² showed that all balcinrenone/dapagliflozin doses used in that study resulted in numerical beneficial effects on UACR and other efficacy variables. The data show potential for a clinical relevant reduction in UACR with balcinrenone/dapagliflozin compared to dapagliflozin with the doses selected in the current study.

2.3.3 Overall Benefit/Risk Conclusion

Considering the anticipated benefits from treatment with balcinrenone/dapagliflozin compared to treatment with dapagliflozin, and the safety monitoring and measures implemented in the study to minimise the potential risks associated with study participation, the benefit-risk balance for the participants is deemed favourable.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine whether balcinrenone/dapagliflozin is superior to dapagliflozin in reducing albuminuria	Relative change in UACR from baseline to Week 12
Safety	
To evaluate the safety and tolerability of balcinrenone/dapagliflozin compared with dapagliflozin	• Occurrence and time to first occurrence of AE, SAE, SAE with outcome death, AE leading to discontinuation of IMP and possibly related AE as assessed by the investigator • Observed laboratory values and changes from baseline • Observed vital sign values (including BP and pulse rate) and changes from baseline • Observed ECG parameters and changes from baseline • Occurrence and time to first event of AESI (hyperkalaemia, renal events/AKI, and hypotension)
Exploratory	
To assess the dose response relationship of balcinrenone/dapagliflozin doses on albuminuria	Relative changes from baseline in UACR over time (analyses will be reported outside of the CSR)
To explore the magnitude of albuminuria regression from balcinrenone/dapagliflozin compared to dapagliflozin	• A > 1-step regression in albuminuria stage (ie, from A3 to A2; from A3 to A1; or from A2 to A1) from baseline • At least a 30% and 50% reduction in albuminuria from baseline
To assess the effect of balcinrenone/dapagliflozin compared with dapagliflozin, on serum K ⁺	Observed values and changes from baseline in serum K ⁺ over time
To assess changes in eGFR over time from baseline to end of study	Observed values and changes in eGFR from baseline during randomised treatment period and after end of treatment
To assess the pharmacokinetics of different doses of balcinrenone/dapagliflozin and of dapagliflozin in plasma	Plasma concentrations of balcinrenone and dapagliflozin over time
To assess the dose response relationship of balcinrenone/dapagliflozin doses on serum K ⁺ and eGFR	Dose/exposure of balcinrenone/dapagliflozin relative to serum K ⁺ and eGFR (analyses will be reported outside of the CSR)
To assess the effect of balcinrenone/dapagliflozin on BP compared with dapagliflozin	Observed values and changes from baseline in SBP and DBP over time

Table 3 Objectives and Endpoints

Objectives	Endpoints
To assess the effect of balcinrenone/dapagliflozin on cardio-renal biomarkers compared to dapagliflozin	Change from baseline to 4 and 12 weeks of plasma protein levels assessed by a multiplex proximity extension assay panel (Olink Explore 3072) (analyses will be reported outside of the CSR)

Primary estimand

The primary clinical question of interest is:

- Is balcinrenone/dapagliflozin 40 mg/10 mg once daily, compared with dapagliflozin 10 mg once daily, more effective in reducing albuminuria as assessed by the relative change from baseline in UACR in adults with CKD and albuminuria by Week 12 and if so, is also balcinrenone/dapagliflozin 15 mg/10 mg once daily, compared with dapagliflozin 10 mg once daily, more effective in reducing albuminuria as assessed by the relative change from baseline in UACR in adults with CKD and albuminuria by Week 12?

The primary estimand is described by the following attributes:

- Population: participants with an established diagnosis of CKD, eGFR between ≥ 25 and < 60 mL/min/1.73 m², and UACR > 100 mg/g to ≤ 5000 mg/g. Participants should not be taking an MRA.
- Endpoint: relative change in UACR from baseline to Week 12.
- Treatment condition: once daily balcinrenone/dapagliflozin 15 mg/10 mg, balcinrenone/dapagliflozin 40 mg/10 mg, or dapagliflozin 10 mg, all given on top of other SoC medications for CKD.
- Population-level summary: geometric mean.
- Intercurrent events handling strategies: intercurrent events of initiation or change in concomitant treatment and discontinuation of IMP will be handled using the treatment policy strategy, while death, initiation of dialysis or kidney transplant, withdrawal of consent, and lost-to-follow-up will be handled using the hypothetical strategy.

The primary objective will be addressed by an estimand ([EMA-I CHE9-R1 2020](#)), which assesses differences in outcomes in treatment groups over the period from randomisation until Week 12, to reflect the effect of the initially assigned randomised IMP, irrespective of concomitant treatment, or discontinuation of IMP, and in the absence of death, initiation of dialysis or kidney transplant, withdrawal of consent, and lost-to-follow-up.

All efforts will be made to the extent possible to follow randomised participants and to collect data regardless of study intervention compliance and use of concomitant medications.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase IIb, multicentre, randomised, double-blind, dose-finding, parallel group, double-dummy study aiming to determine the effect on albuminuria, as well as safety and tolerability of balcinrenone/dapagliflozin compared to dapagliflozin, when given once daily on top of other SoC to patients with CKD and albuminuria.

At least 300 participants ≥ 18 years old, with $\text{eGFR} \geq 25$ to < 60 mL/min/1.73 m², $\text{UACR} > 100$ to ≤ 5000 mg/g, with or without T2DM will be randomised. Participants are eligible both if they are treated or untreated with an SGLT2 inhibitor at screening/enrolment.

Participants will be stratified by:

- eGFR at screening (≥ 25 to < 45 and ≥ 45 to < 60 mL/min/1.73 m²)
- SGLT2 inhibitor treatment at screening (yes/no)
- T2DM status at screening (yes/no)

Participants will be randomised into one of 3 treatment arms in a 1:1:1 ratio:

- Balcinrenone/dapagliflozin 15 mg/10 mg
- Balcinrenone/dapagliflozin 40 mg/10 mg
- Dapagliflozin 10 mg

For each participant, the total duration of participation will be approximately 23 weeks: an up to 3-week screening period followed by a 12-week treatment period, and a 8-week follow-up period after end of IMP treatment. An optional pre-screening visit may be scheduled. The day of the pre-screening visit will be at the discretion of the investigator.

The study will be conducted at approximately 110 sites in approximately 16 countries globally.

4.1.1 Optional Pre-screening

Participants who perform the optional pre-screening visit to evaluate UACR, creatinine and/or eGFR should sign a separate, abbreviated ICF. Samples should be obtained for analysis in a local laboratory. Patient information and laboratory results related to pre-screening visits will be documented at site only ie, not in the study database. Collection of safety information during the pre-screening period will only consist of SAEs related to pre-screening procedures (Section 8.4.8).

4.2 Scientific Rationale for Study Design

This is a dose-finding study aiming to identify an optimal dose of balcinrenone in combination with dapagliflozin for a future Phase III study in patients with CKD with eGFR ≥ 25 to < 60 mL/min/1.73 m² and UACR > 100 mg/g to ≤ 5000 mg/g.

The primary endpoint (relative change in UACR) is a predictive marker of clinical outcome of CKD. A recent large meta-analysis of clinical trials supports reduction of UACR as a predictive marker of clinical outcome in CKD (Levey et al 2020), and individual clinical studies demonstrated a clear dose-dependent effect of MRAs (eg, finerenone) to reduce UACR (Bakris et al 2020).

This study will evaluate general safety and tolerability of balcinrenone/dapagliflozin compared to dapagliflozin with special attention to hyperkalaemia, renal events/AKI, and hypotension.

4.3 Justification for Dose

Two combination doses, balcinrenone/dapagliflozin 15 mg/10 mg and balcinrenone/dapagliflozin 40 mg/10 mg, will be compared with dapagliflozin 10 mg.

The dapagliflozin dose of 10 mg once daily is approved in several indications including treatment of CKD, irrespective of diabetes status, and has a well established safety profile (DAPA-CKD study [Heerspink et al 2020]).

The primary endpoint in the MIRACLE (D6402C00001) Phase II study, relative change in UACR, is an established efficacy marker of MR-related mechanism of action, and has been shown to be predictive for CKD progression (Levey et al 2020), as well as adverse cardiac and HF outcomes for MRAs (TOPCAT study [Selvaraj et al 2018] and FIGARO-DKD study [Pitt et al 2021]). The MIRACLE (D6402C00001) study, evaluating different doses of balcinrenone in combination with dapagliflozin versus dapagliflozin in patients with HF and CKD, showed that all tested doses of balcinrenone resulted in a numerical reduction in UACR (change of geometric mean from baseline at week 12 of -56.4, -42.1 and -58% for 15, 50, and 150 mg doses [combined with 10 mg dapagliflozin], respectively), which may be clinically relevant when compared with dapagliflozin (-34.3% reduction at Week 12). Although the small sample size did not allow for establishment of a clear efficacy dose response relationship, the CCI assessment indicated that 15 and 40 mg may be CCI in terms of CCI. It is therefore anticipated that this CCI may lead to CCI between the 2 proposed doses. In addition, a dose response model for effect on CCI of balcinrenone in combination with 10 mg dapagliflozin was developed based on data from the MIRACLE (D6402C00001) study. The model predicted dapagliflozin-adjusted effects on CCI for the 15 and 40 mg balcinrenone doses, combined with dapagliflozin, were CCI (90% CI: CCI to CCI) and CCI (90% CI: CCI to CCI).

CCI

Based on PK results from patients with severe renal impairment (Study D6401C00008), the balcinrenone exposure (AUC) is predicted to be < 50% higher in a typical patient with an eGFR of 25 mL/min/1.73 m², compared to a typical patient with an eGFR of 60 mL/min/1.73 m². Thus, there is no dose adjustment of balcinrenone in patients with eGFR between 25 and 60 mL/min/1.73 m².

For details, refer to the IB for balcinrenone.

There is a low risk for metabolic drug-drug interactions between dapagliflozin and balcinrenone. Dapagliflozin is mainly eliminated by UGT1A9-mediated metabolism, of which balcinrenone is not an inhibitor or an inducer. Dapagliflozin is not an inhibitor or inducer of CYP3A4-mediated metabolism, which is the major metabolic pathway for balcinrenone (Kasichayanula et al 2012).

4.4 End-of-study Definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last participant for any protocol-related activity.

Food and Drug Administration requirements defines 2 completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if they have completed all phases of the study including CCI Follow-up 2 (Visit 8).

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

- 1 Participant must be ≥ 18 years old, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

- 2 Diagnosis of CKD and $\text{eGFR} \geq 25$ to < 60 mL/min/1.73 m² at screening (Visit 1) (2021 CKD-EPI creatinine formula, analysed at central laboratory).
- 3 $\text{UACR} > 100$ mg/g (10 mg/mmol) to ≤ 5000 mg/g (500 mg/mmol) at screening (Visit 1) (spot urine sample, analysed at central laboratory).
- 4 Serum potassium ≥ 3.5 mmol/L to ≤ 5.0 mmol/L at screening (Visit 1) (analysed at central laboratory).
- 5 Participants treated with RAAS inhibitors must be on a stable dose for at least 4 weeks before screening. Participants who cannot tolerate or are not treated with RAAS inhibitors can also participate in the study.

Sex and Contraceptive/Barrier Requirements

- 6 Contraceptive use by females should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
 - (a) Females not of childbearing potential are defined as females who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age specific requirements apply:
 - (i) Females < 50 years old are considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle-stimulating hormone levels in the postmenopausal range.
 - (ii) Females ≥ 50 years old are considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
 - (b) Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can

achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilised male partner must agree to use one highly effective method of birth control, as defined below, from enrolment throughout the study and until at least 4 weeks after last dose of study intervention.

- (c) The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea. Female condom and male condom should not be used together.
- (d) All WOCBP must have a negative serum pregnancy test result at Visit 1.
- (e) Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study interventions) [periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomised partner, Implanon[®], bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera[™] injections, oral contraceptive associated with inhibition of ovulation, and Evra Patch[™], Xulane[™], or NuvaRing[®].

Informed Consent

- 7 Capable of giving signed informed consent as described in [Appendix A](#) which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. NOTE: For the optional pre-screening visit there is a separate, abbreviated ICF (refer to Section [4.1.1](#)).

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

Cardiac, vascular, and renal conditions

- 1 Uncontrolled arterial hypertension (ie, mean of 3 consecutive measurements of SBP > 160 mmHg or DBP > 100 mmHg) at screening (Visit 1).
- 2 Hypotension defined as mean of 3 consecutive measurements of SBP < 100 mmHg at screening (Visit 1).

- 3 Acute coronary syndrome (myocardial infarction or unstable angina), stroke, transient ischaemic attack within 12 weeks prior to randomisation (Visit 2).
- 4 Diagnosis of lupus nephritis or antineutrophil cytoplasmic antibody-associated vasculitis. Other nephropathies that are unstable, or progress rapidly, or require cytotoxic or immunomodulatory therapy.
- 5 Diagnosis of autosomal dominant polycystic kidney disease.
- 6 Recent (within 90 days prior to screening) or ongoing dialysis, or in the opinion of the investigator likely need for dialysis within 3 months following randomisation (Visit 2).

Other conditions

- 7 Hepatic disease, including active HBV or HCV infection, or other cause of hepatitis, and/or hepatic impairment (Child-Pugh class B-C; or any of AST or ALT $> 3 \times$ ULN; or TBL $> 2 \times$ ULN at time of screening [Visit 1]).
- 8 T1DM or uncontrolled T2DM (HbA1c $> 12\%$ at screening [Visit 1], central laboratory analysis).
- 9 Adrenal insufficiency (eg, Addison's disease, prolonged use of glucocorticoids).
- 10 Serum $\text{HCO}_3^- < 18$ mmol/L at screening (Visit 1) (analysed at central laboratory).
- 11 History of solid organ or bone marrow transplant or plan for it within 6 months following randomisation (including kidney transplant).
- 12 Cytotoxic or immunomodulatory therapy within 6 months prior to screening, or current, or planned within 6 months following randomisation (Visit 2).
- 13 Any of the following related to COVID-19 infection:
 - (a) Suspected (as judged by PI) or confirmed COVID-19 infection within the last 4 weeks prior to screening (Visit 1) or at randomisation (Visit 2).
 - (b) Hospitalisation for COVID-19 within the last 12 weeks prior to screening (Visit 1).
- 14 Any clinically significant disease or condition which, as judged by the investigator or AstraZeneca, might put the participant at risk or confound the interpretation of results because of participation in the study.
- 15 History of malignancy within the last 5 years, excluding successful treatment of basal or squamous cell skin carcinoma or in situ carcinoma of the cervix.

Prior/Concomitant Therapy

- 16 Any use of the following medications and supplements:
 - (a) MRA within 4 weeks prior to screening (Visit 1) or planned initiation of MRA treatment. For participants with a guideline recommendation for MRA, there should be an appropriate rationale in the opinion of the investigator for not using or planning to use an MRA for the duration of the study.

- (b) Potassium sparing diuretics (eg, amiloride, triamterene) within 4 weeks prior to screening (Visit 1).
- (c) Potassium binders within 4 weeks prior to screening (Visit 1).
- (d) Aldosterone analogue fludrocortisone within 4 weeks prior to screening (Visit 1).
- (e) Strong or moderate inducers or inhibitors of CYP3A4, prohibited at least one week prior to randomisation (Visit 2) and for the IMP duration (see [Appendix F](#) for a list of relevant medications and substances).

Prior/Concurrent Clinical Study Experience

- 17 Participation in another clinical study with a study intervention administered within 4 weeks prior to screening (Visit 1).
- 18 Known hypersensitivity to balcinrenone or dapagliflozin or any of the excipients of the product.

Other Exclusions

- 19 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
- 20 Judgement by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.
- 21 Previous enrolment in the present study (does not apply to re-screening of prior one-time screen failures).
- 22 For females only - currently pregnant (confirmed with positive pregnancy test) or breast-feeding.

5.3 Lifestyle Considerations

Participants should be counselled about lifestyle practices that are proper for their medical conditions (eg, kidney disease, T2DM, hypertension), tailored to the individual, and consistent with local guidelines.

5.3.1 Meals and Dietary Restrictions

Participants must avoid grapefruit and grapefruit juice, pomelo, and pomelo juice consumption during the study in order to avoid CYP3A4 inhibition ([Appendix F](#)). There are no other specific meals and dietary restrictions.

5.3.2 Restrictions During the Study

Study medications should be taken at approximately the same hour each morning.

On days when participants will attend the study site for a study visit, they will be asked to **not** take their study medications prior to attending the study visit. The participant will take the study medication at the site, provided they are permitted to continue study intervention following assessments.

Participants should be instructed to contact the site in case of signs of acute illnesses that may increase risk of hyperkalaemia or acute kidney injury (eg, fever, vomiting, diarrhoea, malaise, and/or dehydration). Additional medical check-up and safety samples to be requested at the discretion of the investigator.

Participants with diabetes who experience rapid onset of fatigue, abdominal pain, severe thirst, shortness of breath, and/or vomiting should be instructed to hold IMP until DKA has been ruled out.

5.4 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned the same participant number as for the initial screening.

BP and laboratory parameters may vary in daily life and in case a participant fails to meet eligibility criteria for BP, eGFR, UACR, or serum K⁺, sites are allowed to perform an optional, additional BP measurement or central laboratory assessment within the Visit 1 window before the randomisation visit. This retest does not require participant to re-consent.

5.5 Criteria for Temporarily Delaying Enrolment/Randomisation/Administration of Study Intervention

Not applicable.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all pre-specified, IMPs and NIMPs, medical devices and other interventions (eg, surgical and behavioural) intended to be administered to the study participants during the study conduct.

6.1 Study Intervention(s) Administered

In this double-dummy design, study participants will be randomly assigned in a 1:1:1 ratio to receive once daily administration of one capsule and one tablet of one of the following study interventions:

- Balcinrenone/dapagliflozin 15 mg/10 mg capsule and matching placebo for dapagliflozin 10 mg tablet
- Balcinrenone/dapagliflozin 40 mg/10 mg capsule and matching placebo for dapagliflozin 10 mg tablet
- Dapagliflozin 10 mg tablet and matching placebo for balcinrenone/dapagliflozin capsule

There is one placebo capsule to match both fixed-dose strengths of the balcinrenone/dapagliflozin combination capsule, and one placebo tablet to match the dapagliflozin tablet.

Information about the study interventions is summarised in [Table 4](#).

Table 4 Study interventions

Arm name	Balcinrenone/ dapagliflozin 15 mg/10 mg	Balcinrenone/ dapagliflozin 40 mg/10 mg	Dapagliflozin 10 mg
Intervention name	Balcinrenone/ dapagliflozin 15 mg/10 mg and matching placebo for dapagliflozin 10 mg	Balcinrenone/ dapagliflozin 40 mg/10 mg and matching placebo for dapagliflozin 10 mg	Dapagliflozin 10 mg and matching placebo for balcinrenone/ dapagliflozin
Type	Drug	Drug	Drug
Dose formulation	Capsule + Tablet	Capsule + Tablet	Capsule + Tablet
Unit dose strength(s)	15 mg/10 mg	40 mg/10 mg	10 mg
Dosage level(s)	1 capsule balcinrenone 15 mg and dapagliflozin 10 mg (once daily)	1 capsule balcinrenone 40 mg and dapagliflozin 10 mg (once daily)	1 tablet dapagliflozin 10 mg (once daily)

Table 4 Study interventions

	+ 1 tablet placebo (once daily)	+ 1 tablet placebo (once daily)	+ 1 capsule placebo (once daily)
Route of administration	Oral	Oral	Oral
Use	Experimental	Experimental	Active comparator
IMP or NIMP/AxMP	IMP	IMP	IMP
Sourcing	Balcinrenone/dapagliflozin, dapagliflozin and their matching placebo will be supplied centrally through AstraZeneca.		
Packaging and labelling	Study Intervention will be provided in bottles. Each bottle will be labelled as required per country requirement.		

Label text prepared for balcinrenone/dapagliflozin will show the name ‘balcinrenone and dapagliflozin’ or ‘balci and dapa’ or ‘AZD9977 and dapagliflozin’, with slight variations, depending upon the agreed name used in the approved study master label document. All naming conventions are correct during this transitional period.

6.1.1 Medical Devices Including Combination Products with a Device Constituent

No AstraZeneca manufactured medical devices (or devices manufactured for AstraZeneca by a third party) are provided for use in this study.

6.2 Preparation, Handling, Storage, and Accountability

- The investigator or designee must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received at the site and throughout the entire study until authorisation is provided for on-site destruction or removal of the IMP, reflecting completion of the study. In the event of a temperature excursion detected at any time during the study, sites will follow the reporting procedures for notifying AstraZeneca; release of IMP for clinical use can only occur once the event has been reviewed and approval is provided by AstraZeneca.
- Only participants randomised in the study may receive study intervention, and only authorised site staff may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator, institution, the head of the medical institution (where applicable), is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3 Assignment to Study Intervention

All participants will be centrally assigned to randomised study intervention using an IRT/RTSM. Before the study is initiated, log in information and directions for the RTSM will be provided to each site.

Randomisation will be stratified in IRT/RTSM based on participant's laboratory eGFR category (≥ 25 to < 45 and ≥ 45 to < 60 mL/min/1.73 m²), SGLT2 inhibitor use at screening (yes/no), and T2DM status at screening (yes/no).

Study intervention will be dispensed and returned at the study visits summarised in SoA (Table 1). Collected study intervention should not be re-dispensed to the participants.

6.4 Blinding

The IRT/RTSM will provide to the investigators or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT/RTSM user manual that will be provided to each centre.

The IRT/RTSM will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, AstraZeneca must be notified within 24 hours after breaking the blind. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to the participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to a study intervention and that potentially require expedited reporting to regulatory authorities. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

AstraZeneca safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or AstraZeneca policy.

PK samples will be analysed by the bioanalytical laboratory performing the bioanalyses only for participants on active treatment, as referenced in Section 8.5. To allow for the appropriate selection of samples, the bioanalytical laboratory will, therefore, have access to the treatment codes but will not share the codes with AstraZeneca or others involved in the study until the blinding is broken for the study.

The DMC will receive unblinded study data for safety review. These data will be defined in the DMC charter. Further details are provided in Section 9.6.

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6.5 Study Intervention Compliance

Participants will take treatment at the site on visit days and at home between visits.

When participants are dosed at the site, they will receive study interventions directly from the investigator or designee, under medical supervision, after checking treatment was not taken at home before coming to the study site.

When participants self-administer study interventions at home, compliance with study interventions will be assessed at each visit by direct questioning and counting returned tablets/capsules. The participants will be asked regarding the time of their last IMP intake prior to PK sampling and if the IMP was taken with food ie, taken before breakfast or other first meal. Information will be documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of dapagliflozin tablets and balcinrenone/dapagliflozin capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for temporary interruptions will also be recorded in the eCRF.

6.6 Dose Modification

No dose modifications are allowed during the study.

6.7 Continued Access to Study Intervention After the End of the Study

No study intervention will be provided after the end of the study.

6.8 Treatment of Overdose

Dapagliflozin has been well tolerated at doses up to 500 mg/day in single dose testing in healthy volunteers and up to 100 mg/day in repeat dose testing for 14 days in healthy

volunteers and participants with T2DM. Only suspected single intake of more than 500 mg dapagliflozin or repeated intake of more than 100 mg dapagliflozin should be reported on the eCRF overdose module.

Presently there is no information regarding overdose of balcinrenone in man. For this study, any intake of more than one capsule of balcinrenone/dapagliflozin (or matching placebo) once daily is to be considered an overdose.

In the event of an overdose, the investigator should:

- Evaluate the participant to determine, in consultation with the Study Clinical Lead, if possible, whether study intervention should be interrupted.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up. Refer to Section 8.4.11 for details of AE/SAE reporting related to overdose.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.9 Prior and Concomitant Therapy

Participants treated with an SGLT2 inhibitor prior to enrolment into the study will be switched to dapagliflozin at randomisation as part of the study intervention (Section 6.1). After ending the randomised treatment period of the study, these participants should resume their pre-study SGLT2 inhibitor therapy starting one day after the last dose of study medication (unless considered by the investigator being unsafe for the participant).

Participants are expected to be on SoC (except for MRA treatment) according to local guidelines for impairment of kidney function at enrolment, along with SoC for any other concomitant disease (for example, T2DM, hypertension etc).

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of screening (Visit 1) or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Clinical Lead should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1 Medications Inducing Hypoglycaemia

Insulin and insulin secretagogues, such as sulfonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with dapagliflozin in patients with T2DM.

In participants with normal blood glucose and/or low GFR, dapagliflozin has a low propensity to cause hypoglycaemia, as the amount of filtrated glucose is small and can be reabsorbed by SGLT1 and unblocked SGLT2 transporters.

6.9.2 Prohibited Medications

The medications listed below are prohibited during the study:

- MRAs or aldosterone antagonists (eg, eplerenone, finerenone, spironolactone).
- Potassium sparing diuretics (eg, amiloride, triamterene).
- Aldosterone analogue fludrocortisone.

The medications listed below are prohibited during the randomised treatment period:

- SGLT2 inhibitors, other than the IMP.
- Strong or moderate CYP3A4 inhibitors or inducers (see [Appendix F](#) for a list of relevant medications and substances).

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are handled as part of [Appendix A](#).

AstraZeneca designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of AstraZeneca. For details see [Appendix A 9](#).

7.1 Discontinuation of Study Intervention

Note that discontinuation from study intervention is *not* the same thing as a discontinuation or withdrawal from the study (Section [7.2](#)).

If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study, ie, continue to participate in the subsequent scheduled study visits and evaluations. If the participant agrees a modified follow-up can be applied, see Section [7.2](#). The investigator should use his or her medical judgement as to the most appropriate medication the participant should take for the remainder of the study duration. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

If the IMP is permanently discontinued, the PTDV assessments should be performed as soon as possible (and preferably within 2 weeks; see SoA [[Table 1](#)]).

7.1.1 Temporary Interruptions

Participants should be temporarily interrupted from IMP in the following situations:

- If at any time during the study, the investigator decides that the participant must be treated transiently with any strong or moderate CYP3A4 inhibitor or inducer ([Appendix F](#), [Table 8](#)).
 - For strong or moderate CYP3A4 inhibitor or inducer treatment, IMP may be restarted one week after the strong or moderate CYP3A4 inhibitor or inducer treatment was suspended, given that the treatment lasted ≤ 4 weeks.
- Hyperkalaemia.

Hyperkalaemia should be managed as per local SoC. For reporting of AEs based on laboratory values of hyperkalaemia see Section [8.4.5](#).
Study specific interruption criteria and management regarding potassium are described below.

 - If potassium is > 5.5 to ≤ 6.0 mmol/L, the participant may remain on IMP, however the potassium should be re-checked within 72 hours, and if confirmed > 5.5 mmol/L, IMP should be temporarily interrupted.

- If potassium is > 6.0 mmol/L, immediately temporarily interrupt IMP treatment, manage as per local SoC and re-check potassium within 72 hours.
- IMP may be restarted when potassium is ≤ 5.0 mmol/L, and potassium should then be re-checked by central laboratory within 2 to 7 days of restart.
- Decline in kidney function.
If an unexpected, acute or subacute decline in kidney function is observed, the participant should be evaluated. Volume depletion, hypotension, intercurrent medical problems or concomitant drugs may cause an acute decrease in kidney function. Urinary tract infection and urinary obstruction should be considered (the latter especially in men). Several drugs may impact kidney function or creatinine levels, especially non-steroidal anti-inflammatory drugs, cimetidine, and certain antibiotics such as trimethoprim.
For reporting of AEs related to impaired kidney function see Section 8.4.4.
Study specific interruption criteria and management regarding declining kidney function will be as follows:
 - In case of a $\geq 57\%$ decrease in eGFR since the prior visit (or doubling of serum creatinine), immediately temporarily interrupt IMP treatment, and the participant should be treated as per local SoC; samples for central analysis of serum creatinine or eGFR should be re-checked as soon as possible and always within 96 hours.
 - IMP may be restarted when the serum creatinine/eGFR level has improved and stabilised in the opinion of the investigator. Kidney function and serum K^+ should be closely monitored after IMP is restarted, at the discretion of the investigator.
- DKA:
Temporary interruption of IMP should be considered if DKA is suspected and the participant should be promptly evaluated:
 - If DKA is confirmed, IMP should be permanently discontinued.
 - If DKA is not confirmed, IMP may be restarted.

7.1.2 Permanent Discontinuation

Participants may be permanently discontinued from IMP in the following situations:

- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment.
- AE. An AE that, in the opinion of the investigator, warrants discontinuation from further dosing.
- Severe noncompliance with the CSP.

- Investigator decision. Reasons, other than AE, as judged by the investigator where treatment should not be continued.
- Pregnancy. If the participant becomes pregnant during the course of the study, permanently discontinue IMP.
- Development of study specific discontinuation criteria, ie, in case of confirmed DKA or recurrent hyperkalaemia (potassium > 6.0 mmol/L) within 4 weeks of restarting IMP after its temporary interruption, provided no plausible explanation other than use of IMP exists for the recurrent event.
- Treatment with an MRA, irrespective if temporary or permanent.
- Kidney transplant.
- Additional reasons could be study terminated by AstraZeneca or other reasons not listed above.

7.1.3 Procedure for Erroneously Randomised Participants

A situation might arise where, despite every effort, a participant is randomised into the study while not fulfilling one or several of the inclusion/exclusion criteria. In this case, the following steps should be undertaken:

- 1 The AstraZeneca Physician should be contacted for an assessment of whether study intervention could pose a risk to the participant in light of the new information.

If yes, the participant should be immediately discontinued from study intervention (not to be confused with participant withdrawal from the study).

If no, the AstraZeneca Physician should carefully review the specific inclusion/exclusion criterion which was not met. If discontinuation of study treatment is deemed detrimental to the participant, the study medication will be continued and the decision documented. If discontinuation of study medication is not detrimental to the participant, it will be discontinued, the participant followed according to the study protocol, and the decision documented.

The occurrence should be documented as an important/major protocol deviation.

7.2 Participant Discontinuation/Withdrawal From the Study

Discontinuation of the participant from the study by the investigator:

- A participant may be discontinued from the study at any time at the discretion of the investigator for compliance reasons.
- At the time of discontinuing from the study, if the IMP was not previously prematurely discontinued, if possible, a PTDV should be conducted (Section 7.1).

Voluntary withdrawal from the study by the participant:

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant who wishes to withdraw from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- If the participant withdraws consent for disclosure of future information, AstraZeneca may retain and continue to use any data collected before such a withdrawal of consent.
- If the participant withdraws from the study, AstraZeneca may retain and continue to use any samples collected before such a withdrawal of consent for the purposes the participant originally consented unless the participant withdraws consent for use of samples already collected. If the participant specifically withdraws consent for any use of samples, it must be documented in the site study records by the investigator, and the investigator must inform the Local and Global Study Team. Destruction of any samples collected and not yet tested should be carried out in line with documented sample withdrawal wishes in conjunction with what was stated in the informed consent and local regulation.

If a participant withdraws from the study, then his/her enrolment or randomisation code(s) cannot be reused. Withdrawn participants will not be replaced.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The participant should be counselled on the importance of maintaining the assigned visit schedule. At this time ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, telephone calls, texts, emails, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable after 3 documented attempts, the participant will be considered to have been lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA ([Table 1](#)). Protocol waivers or exemptions are not allowed.
- Urgent safety concerns should be discussed with AstraZeneca immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA ([Table 1](#)), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Instructions for the collection and handling of HBS will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on handling of HBS see [Appendix C](#).

In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by AstraZeneca or the investigator, as per local health authority/ethics requirements.

8.1 Administrative Procedures

All administrative and general/baseline procedures are outlined in the SoA ([Table 1](#)) and not described in the subsequent sections.

8.2 Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA ([Table 1](#)).

8.2.1 Primary Variable - Urinary Albumin-to-Creatinine Ratio

The UACR is calculated as follows:

- $\text{UACR [mg/g]} = \text{urine albumin [mg/dL]} / \text{urine creatinine [g/dL]}$

Urine samples for the determination of albumin and creatinine, and calculation of UACR will be collected at the timepoints described in the SoA ([Table 1](#)):

- For screening (Visit 1), one random spot urine specimen should be collected during the visit and analysed centrally.

- For baseline (Visit 2), Visit 4, Visit 5 and Visit 6 participants will be instructed to collect a first morning void urine sample preferably on 3 consecutive days prior to the visit (preferably the day of visit and the preceding 2 days) which will be returned on the day of visit. Samples should be refrigerated until returned to the site.

All efforts should be made to ensure morning void samples are properly collected. Only in exceptional circumstances where participant arrives to site without any morning void samples, a spot urine sample can be collected during the visit and reported as an extra urine sample for UACR analysis. Samples will be analysed centrally.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA ([Table 1](#)).

8.3.1 Physical Examinations

A complete physical examination will be performed and include assessments of general appearance, respiratory, cardiovascular, abdominal and neurological systems, the skin, lymph nodes, and an assessment of the presence and extent of peripheral (ankle/leg) oedema.

Physical examination will be performed at timepoints as specified in the SoA ([Table 1](#)).

For information on how AEs based on physical examination findings should be recorded and reported, see Section [8.4.5](#).

8.3.2 Body Weight and Height

For weight, the participant will be allowed to wear indoor, daytime clothing with no shoes and no coats/jackets and removal of heavy objects from pockets. Weight will be recorded in the eCRF.

The participant's height will be measured without shoes. Height will be recorded in the eCRF.

Body weight and height will be assessed at timepoints as specified in the SoA ([Table 1](#)).

8.3.3 Vital Signs

BP and pulse rate will be assessed at the study site, as outlined in the SoA ([Table 1](#)), prior to blood collection for laboratory tests with the participant resting in a supine or seated position, on the same arm and same position consistently throughout the study using an automated device. Manual techniques will be used only if an automated device is not available.

BP and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones) and will consist of one pulse and 3 BP measurements (3 consecutive BP readings will be recorded at intervals of at least one minute). The average of the 3 BP readings will be recorded on the eCRF.

Vital signs will be assessed at timepoints as specified in the SoA ([Table 1](#)).

For information on how AEs based on vital sign results should be recorded and reported, see Section [8.4.5](#).

8.3.4 Electrocardiograms

12-lead ECGs (standard ECG with a paper speed of 25 to 50 mm/second covering at least 6 sequential beats) should be recorded after the participant has been resting for at least 5 minutes. ECG date, heart rate, heart rhythm, QT, and QTcF intervals will be recorded in the eCRF. All ECG source data should be retained in the participant records and made available to the monitor upon request. All timepoints for ECG recordings are specified in the SoA ([Table 1](#)).

8.3.5 Clinical Safety Laboratory Tests

Local laboratory serum or plasma potassium and eGFR will be assessed for all participants at Visit 3.

The clinical chemistry, haematology, and urinalysis will be performed by a central laboratory throughout the study, as indicated in the SoA ([Table 1](#)).

If clinically indicated, additional safety samples may be collected at the discretion of the investigator, as described in Section [7.1](#). For reporting of abnormalities in local laboratory see Section [8.4.4](#) and Section [8.4.5](#).

The following laboratory variables will be measured ([Table 5](#)):

Table 5 Laboratory Safety Variables	
Clinical Chemistry (serum or plasma) ^a	Haematology/Haemostasis (whole blood) ^a
Serum Na ⁺	White blood cell count
Serum K ⁺ ^b	White blood cell differential count
Blood urea nitrogen	Haemoglobin
Serum creatinine ^b	Haematocrit
eGFR ^{b,c}	Platelets
Uric acid	MCV
Albumin	MCHC
Calcium	HbA1c (at screening and EoT only)
Phosphate	Red blood cell count
Alkaline phosphatase	Urinalysis (urine dipstick) ^a
ALT	Protein
AST	Glucose

Table 5 Laboratory Safety Variables

TBL	Blood
Creatine kinase	Leukocyte esterase
Bicarbonate (HCO ₃ ⁻)	Specific gravity
Chloride (Cl ⁻)	pH
Magnesium (Mg ⁺)	Other assessments
Glucose (non-fasting)	FSH ^a (for confirmation of postmenopausal status of amenorrheic women < 50 years old only [women who are permanently sterilised are exempted], at screening)
	Pregnancy test (WOCBP only) ^d
	RT-PCR test for SARS-CoV-2 to be performed locally (if required by local authorities)

NB. In case a participant shows an AST **or** ALT $\geq 3 \times \text{ULN}$ together with TBL $\geq 2 \times \text{ULN}$ please refer to [Appendix D](#), for further instructions.

- ^a Central laboratory.
- ^b Central laboratory at all visits, additional local laboratory testing at Visit 3 as specified in the SoA ([Table 1](#)).
- ^c eGFR will be calculated from central laboratory creatinine specimens, using the 2021 CKD-EPI creatinine formula ([Inker et al 2021](#)), and reported as mL/min/1.73 m².
- ^d Serum test at screening/enrolment (for determination of eligibility), urine test at randomisation/pre-dose and EOTV/PTDV. Ad hoc test to be used at the discretion of investigators during the treatment period in case of suspected pregnancy. If required by local authorities, additional pregnancy test can be done during the study and urine pregnancy test can be replaced by a local laboratory blood pregnancy test.

Instructions for the collection and handling of the samples will be provided in the study specific Laboratory Manual.

8.4 AEs, SAEs, and Other Safety Reporting

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in [Appendix B](#).

Participants (or, when appropriate, a caregiver, surrogate, or the participant's legally authorised representative) will notify the investigator or designees of symptoms. These must then be assessed by the investigator and if considered an AE it will be reported by the investigator.

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

AE variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IMP(s) (yes or no)
- Action taken with regard to IMP(s)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE description
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

AEs will be collected from randomisation throughout the treatment period and including the follow-up period.

SAEs will be recorded from the time of signing of the ICF.

For participants undergoing a pre-screening visit, SAE information related to pre-screening study procedures only will be collected from the time of signing the optional pre-screening ICF (abbreviated) until end of pre-screening visit.

If the investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a treated participant, the investigator shall, without undue delay, report the SAE to AstraZeneca.

8.4.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.4.3 Causality Collection

The investigator should assess causal relationship between each of the IMP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in [Appendix B](#).

8.4.4 Adverse Events of Special Interest

For details on the analyses of the AESIs, see Section [9.4.3.1](#).

Investigator-reported information related to the AESIs (as defined below) will be recorded on specific eCRF pages. For analysis of investigator-reported AEs, a list of predefined PTs for each of the AESIs is included in [Appendix G](#). For reporting of AEs based on laboratory values or BP values, see Section [8.4.5](#).

Hyperkalaemia

Protocol-defined criteria for hyperkalaemia:

- Central laboratory post-baseline serum K⁺ levels above the thresholds of 5.5 mmol/L and 6.0 mmol/L.
- Investigator-reported local laboratory post-baseline serum or plasma K⁺ levels above the thresholds of 5.5 mmol/L and 6.0 mmol/L.

Renal Events/AKI

Protocol-defined criteria for renal events related to ESKD:

- Maintenance dialysis for ≥ 28 days, OR
- Kidney transplant, OR
- Investigator-reported sustained eGFR of < 15 mL/min/1.73 m² for ≥ 28 days

Protocol-defined criteria for renal events related to AKI (serum creatinine criteria may be based on central or local laboratory):

- Investigator-reported increase in serum creatinine ≥ 2 and < 3 times baseline known or presumed to have occurred in the last 7 days, OR
- Investigator-reported increase in serum creatinine ≥ 3 times baseline known or presumed to have occurred in the last 7 days, OR
- Use of temporary dialysis (up to 28 days).

Hypotension

Protocol-defined criteria for hypotension:

- Investigator-reported systolic BP below the threshold 90 mmHg and associated symptoms.
- Any post-baseline systolic BP below the threshold 80 mmHg.

8.4.5 AEs Based on Examinations and Tests

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, and ECG findings should only be reported as AEs if they meet any of the following:

- Fulfil any of the SAE criteria
- Are the reason for discontinuation of the IMP
- Are clinically relevant as judged by the investigator (which may include but is not limited to consideration as to whether intervention or non-planned visits were required or other action was taken with the IMP, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia vs low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the DUS.

The results from the protocol-mandated laboratory tests and vital signs will be summarised in the CSR.

8.4.6 AEs Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: ‘Have you had any health problems since the previous visit/you were last asked?’, or revealed by observation will be collected and recorded in the eCRF.

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.4.7 Hy’s Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation, and occurrences of $AST \text{ or } ALT \geq 3 \times ULN$ together with $TBL \geq 2 \times ULN$ may need to be reported as SAEs. Please refer to [Appendix D](#) for further instruction on cases of increases in liver biochemistry and evaluation of Hy’s Law.

8.4.8 Reporting of SAEs

8.4.8.1 Reporting of SAEs at Optional Pre-screening Visit

All SAEs related to the pre-screening study procedures performed during pre-screening visit will be recorded in the participant’s medical record (as no eCRF will be created for pre-screening purposes) and reported using paper SAE Report Form. All pre-screening SAEs will be reported to the AstraZeneca Patient Safety data entry site, in accordance with procedures in [Section 8.4.8.2](#) below.

8.4.8.2 Reporting of SAEs

All SAEs must be reported, whether or not considered causally related to the IMP. All SAEs will be recorded in the eCRF.

If any SAE occurs during the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within**

one calendar day of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it. Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated e-mail alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports the SAE via secure method to the appropriate AstraZeneca representative.

When the EDC is temporarily not accessible, the AstraZeneca Study Representative should confirm that the investigator/site staff enters the SAE in the AstraZeneca EDC when access resumes.

For further guidance on the definition of an SAE, see [Appendix B](#).

The reference document for definition of expectedness/listedness is the IB for both study interventions.

8.4.9 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants

8.4.9.1 Maternal Exposure

If a participant becomes pregnant during the study, study intervention should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives immediately but no later than **24 hours** after he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for pregnancies associated with SAEs (Section 8.4.8) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper based PREGOUT module is used to report the outcome of the pregnancy.

8.4.9.2 Paternal Exposure

There is no restriction on fathering children or donating sperm during the study, and no reporting requirements for pregnancies in partners to male study participants.

8.4.10 Medication Error, Drug Abuse, and Drug Misuse

8.4.10.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (Section 8.4.8) and **within 30 days** for all other events.

8.4.10.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication error can be found in Appendix B 4.

8.4.10.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix [B 4](#).

8.4.10.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix [B 4](#).

8.4.11 Reporting of Overdose

Refer to Section [6.8](#) for definition and treatment of overdose.

- An overdose with associated AEs is recorded as the AE diagnoses/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an IMP or AstraZeneca NIMP occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (Section [8.4.8](#)) and **within 30 days** for all other overdoses.

8.5 Pharmacokinetics

- Pre-dose whole blood samples will be collected for measurement of plasma concentrations of balcinrenone and dapagliflozin as specified in the SoA ([Table 1](#)).
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and AstraZeneca, eg, for urgent safety reasons, and this may be reflected as a protocol deviation.
- The timing of sampling may be altered during the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.
- For storage, re-use, and destruction of samples for PK see [Appendix C](#).

- Pharmacokinetics samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier).
- Additional analyses may be conducted on the anonymised, pooled, or individual PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- No PK samples should be collected from participants after PTDV.

8.5.1 Determination of Drug Concentration

Samples for determination of balcinrenone and dapagliflozin concentrations in plasma will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using appropriately validated bioanalytical methods. Full details of the analytical methods used will be described in a separate Bioanalytical Report.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.6 Pharmacodynamics

Collection and analysis of UACR will be performed as described in Section 8.2.1. No other PD assessments will be performed in this study.

8.7 Optional Genomics Initiative – Not Applicable

Optional Genomics Initiative research is not applicable in this study.

8.8 Biomarkers

8.8.1 Mandatory Biomarker Sample Collection

By consenting to participate in the study the participant consents to the mandatory research components of the study. Collection of mandatory samples for biomarker research is part of this study.

- Plasma samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Table 1).
- Samples will be tested for expression levels of the 3072 proteins included in the Olink Explore 3072 panel. Change in expression levels from baseline to 4 and 12 weeks treatment will be assessed and compared between treatment groups. The results will be reported in a separate report.

- The Olink Explore 3072 biomarker data will not be used for patient management. Results will not be shared at a patient level with the sites.
- Samples for biomarker research will be disposed of after finalisation of the biomarker report.

For storage, re-use, and destruction of biomarker samples see [Appendix C](#).

8.8.2 Optional Biomarker Sample Collection – Not Applicable

Collection of optional samples for biomarker research is not part of this study.

8.9 Immunogenicity Assessments – Not Applicable

Immunogenicity assessments will not be performed in this study.

8.10 Health Economics OR Medical Resource Utilisation and Health Economics – Not Applicable

Health economics/Medical resource utilisation and health economics parameters are not evaluated in this study.

8.11 Study Participant Feedback Questionnaire – Not Applicable

Study Participant Feedback Questionnaires are not applicable for this study.

9 STATISTICAL CONSIDERATIONS

The SAP will be finalised prior to 90 days after randomisation of the first participant and it will include a more technical and detailed description of the planned statistical analyses. This section is a summary of the planned analysis of the primary efficacy endpoint and safety variables.

9.1 Statistical Hypotheses

The primary efficacy hypothesis of the study is that in adults with CKD and albuminuria, balcinrenone/dapagliflozin (either 40 mg/10 mg or both 40 mg/10 mg and 15 mg/10 mg, once daily) is superior to dapagliflozin 10 mg in reducing albuminuria, as assessed by the relative change in UACR from baseline to Week 12.

Each balcinrenone/dapagliflozin arm will be compared to the dapagliflozin arm separately at a one-sided significance level of 5%. Firstly, the high dose-arm will be tested against the comparator, and if successful, the low-dose arm will be tested against the comparator at the second step. The primary hypothesis will be tested using the GM of relative change in UACR from baseline to Week 12. The superiority of balcinrenone/dapagliflozin to dapagliflozin for the primary endpoint will be tested using the hypotheses:

H01: GM [relative change from baseline in balcinrenone 40 mg/dapagliflozin 10 mg] = GM [relative change from baseline in dapagliflozin 10 mg]

versus

H11: GM [relative change from baseline in balcinrenone 40 mg/dapagliflozin 10 mg] $\neq$ GM [relative change from baseline in dapagliflozin 10 mg]

AND

H02: GM [relative change from baseline in balcinrenone 15 mg/dapagliflozin 10 mg] = GM [relative change from baseline in dapagliflozin 10 mg]

versus

H12: GM [relative change from baseline in balcinrenone 15 mg/dapagliflozin 10 mg] $\neq$ GM [relative change from baseline in dapagliflozin 10 mg]

9.2 Sample Size Determination

The sample size determination assumes a 0.7 geometric mean ratio between balcinrenone/dapagliflozin and dapagliflozin relative changes from baseline in UACR, and a standard deviation of 1.0 on log-transformed scale. It is expected that 100 evaluable

participants (participants with baseline and one post-baseline measurements of UACR) per treatment group (300 participants in total) will provide a power of 80% for a one-sided type I error rate of 5% to test the high-dose of balcinrenone/dapagliflozin against dapagliflozin.

9.3 Populations for Analyses

The following populations are defined:

Table 6 Populations for Analysis

Population/analysis set	Description
Enrolled	All participants who sign the ICF. Not applicable to participants who sign the optional pre-screening ICF (abbreviated).
Randomised	All randomised participants.
FAS	All participants who are randomised and receive at least one dose of any IMP. Participants are evaluated according to the treatment assigned at randomisation. The FAS will be used for all analyses (demography, safety, and efficacy).

9.4 Statistical Analyses

9.4.1 General Considerations

Deviations from the protocol will be assessed as important or not important. All protocol deviations will be discussed at the data review meeting and finalised prior to clinical data lock. Important deviations will include the following:

- Violation of inclusion and/or exclusion criteria
- Participants who received the wrong IMP at any time during the study
- Administration of prohibited medications concomitant with IMP

9.4.2 Efficacy

9.4.2.1 Primary Endpoint

Baseline for UACR will be defined as the geometric mean of 3 UACR values derived from first morning void samples collected at 3 consecutive days, the third being the randomisation date (prior to the first dose of IMP).

The primary endpoint is the relative change in UACR from baseline to Week 12. In the analysis of the primary endpoint, treatments (balcinrenone/dapagliflozin 15 mg/10 mg versus dapagliflozin 10 mg and balcinrenone/dapagliflozin 40 mg/10 mg versus dapagliflozin 10 mg) will be analysed assuming that the UACR over time follows a log-normal distribution, hence the observed values will be log-transformed for the analysis. The change from baseline in

log-transformed UACR at Week 12 for each of the 2 doses of balcinrenone combined with dapagliflozin 10 mg and dapagliflozin 10 mg will be estimated in a mixed model for repeated measures including in the model the treatment group, visit, and the treatment-by-visit interaction as fixed effects, adjusting for baseline log-transformed UACR values, randomisation stratification factors, and a participant level random effect. The estimated change from baseline for each treatment arm as well as the difference between the 2 dose arms and dapagliflozin 10 mg arm will be back-transformed onto the original scale to give relative changes from baseline and the relative difference between treatments. Each balcinrenone/dapagliflozin arm will be compared to the dapagliflozin arm CCI at a CCI significance level of CCI the high-dose arm will be tested against the comparator, and CCI the low-dose arm will be tested against the comparator at the CCI

The FAS will be used for the primary efficacy analysis. Sensitivity analyses will be described in the SAP.

9.4.2.2 Exploratory Endpoints

The analysis of exploratory endpoints reported in the CSR will be described in the SAP.

9.4.3 Safety

The general safety objective is to assess the safety and tolerability of balcinrenone/dapagliflozin compared with dapagliflozin in patients with CKD and albuminuria. The general safety objective will be evaluated under on-treatment and on-study (on and off treatment) approaches. All safety analyses will be performed on the FAS. Detailed description of the safety estimand will be provided in the SAP.

Safety and tolerability will be evaluated in terms of AEs, clinical laboratory variables, vital signs, and ECG. In addition, extra evaluation will be done for the following AESIs: hyperkalaemia, hypotension, and renal events/AKI, further specified in the SAP. Exposure to IMP will be described. Analyses will be performed on the FAS.

Occurrence and time to first occurrence of AE, SAE, SAE with outcome death, AE leading to discontinuation of IMP, and any AE possibly related to IMP as assessed by the investigator will be analysed by treatment group. HR comparing treatment groups will be estimated based on a Cox proportional hazards regression model with a factor for treatment group, over the defined analysis period (on-study and on-treatment respectively). For the HR estimate, 95% confidence interval will be obtained from the same model.

The probability of the event of interest occurring before Week 12 will be estimated using the Kaplan-Meier estimator by treatment group for the defined analysis period (on-study and on-treatment respectively). The difference of Kaplan-Meier probabilities between each combination dose-arm and the control arm will be estimated at Week 12. For the estimate of

the difference in probabilities, 95% confidence interval will be obtained.

Observed values and changes from baseline in laboratory values, vital signs, and ECG parameters will be summarised over time by treatment group. In addition, the number and percent of participants with a treatment-emergent abnormality in clinical laboratory tests will be summarised over time by treatment group.

In the analysis of the exposure, frequency and percentages of participant disposition and reasons for discontinuation of IMP will be presented. Participants who prematurely discontinued the IMP will be listed along with the reason for discontinuation. In addition, Kaplan-Meier estimates for time to premature IMP discontinuation will be presented.

All SAEs collected during pre-screening will be recorded in the participant's medical record (as no eCRF will be created for pre-screening purposes). Pre-screening SAEs will be reported to AstraZeneca safety database and be part of routine safety surveillance.

9.4.3.1 Adverse Events of Special Interest

AESIs will be summarised by treatment group. Analysis of investigator-reported AEs will be based on predefined PTs, specified in the SAP and [Appendix G](#), for all AESIs.

Hyperkalaemia

Hyperkalaemia risk will be analysed based on:

- Reported hyperkalaemia AEs, SAEs, and DAEs
- Observed values and change from baseline in serum potassium levels.
- Protocol-defined criteria for hyperkalaemia (Section [8.4.4](#)).
 - Outputs for confirmed values (by another central or local laboratory value, collected within up to 72 hours) and single (not confirmed values) will be presented separately.

Renal Events/AKI

Renal events/AKI will be analysed based on:

- Reported deteriorating renal function-related AEs, SAEs, and DAEs.
- Observed values and change from baseline in serum creatinine/eGFR levels.
- Protocol-defined criteria for renal events/AKI (Section [8.4.4](#)).

Hypotension

Hypotension will be analysed based on:

- Any reported AEs, SAEs, and DAEs due to hypotension.

- Observed values and change from baseline in BP.
- Protocol-defined criteria for hypotension (Section 8.4.4).

9.5

CCI

9.6 Data Monitoring Committee

A DMC consisting of AstraZeneca representatives (who are neither involved in the conduct of the study nor in the balcinrenone/dapagliflozin programme) CCI

CCI is set up for ongoing safety monitoring. In addition to general safety/tolerability, the DMC CCI

For details on the committee, refer to CCI and the CCI

9.7

CCI

An CCI consisting of CCI involved neither in the CCI
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For details CCI and the CCI

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
 - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki as amended at 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
 - Applicable ICH GCP Guidelines
 - Applicable laws and regulations
- The protocol, revised protocol, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any revised protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to AstraZeneca of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All Suspected Unexpected Serious Adverse Reactions (SUSARs) to investigational

medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.

- For all studies except those utilising medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and AstraZeneca policy and forwarded to investigators as necessary.
- Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches of Protocol or GCP

Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal obligations and ethical obligations are met.

- A “serious breach” means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical trial.

AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators.

- Where the EU Clinical Trials Regulation 536/2014 applies, AstraZeneca has in place processes to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.

If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately.

In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.

The investigator should have a process in place to ensure that:

- The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
- A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-investigators will provide AstraZeneca with sufficient, accurate financial information as requested to allow AstraZeneca to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for one year after completion of the study.

A 3 Informed Consent Process

- The investigator or their representative will explain the nature of the study to the participant or their legally authorised representative and answer all questions regarding the study.
- A pre-screening ICF (abbreviated) has to be signed before any pre-screening procedure will take place.
- A ICF (full) has to be signed before any study intervention will take place.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was screened in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- If new information requires changes to the ICF, consider if participants must be re-consented and if so, this must be to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional HBS. The investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples.

A 4 Data Protection

- Participants will be assigned a unique identifier by AstraZeneca. Any participant records or datasets that are transferred to AstraZeneca will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by AstraZeneca in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by AstraZeneca, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.
- The participant must be informed that in some cases their data may be pseudonymised. The General Data Protection Regulation defines pseudonymisation as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Personal Data Breaches

A ‘personal data breach’ means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed.

- In compliance with applicable laws, the Data Controller¹ for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the

¹ The **data controller** determines the **purposes** for which and the **means** by which personal data are processed, as defined by the European Commission.

data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.

- While AstraZeneca has processes in place to deal with personal data breaches it is important that investigators that work with AstraZeneca have controls in place to protect patient data privacy.

The investigator should have a process in place to ensure that:

- allow site staff or service providers delegated by the investigator/institution to identify the occurrence of a (potential) personal data breaches.
- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

AstraZeneca and the site must demonstrate that they:

- have taken all necessary steps to avoid personal data breaches and
- have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

Notification of personal data breach to participants:

- Notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The site and/or Principal Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to

data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants.

- If a personal data breach involving an AstraZeneca's representative device (ie, Study Monitor laptop), AstraZeneca representative will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the participants. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data participants, the notification will be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.
- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

A 5 Committees Structure

Data Monitoring Committee

An unblinded DMC will be set up for this study. The unblinded DMC is a group of AstraZeneca scientists (who are neither involved in the study conduct nor in the balcinrenone/dapagliflozin programme) CCI [REDACTED] who are appointed to monitor the safety of the study. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study. In addition to general safety and tolerability, the committee CCI [REDACTED] CCI [REDACTED]

The DMC is responsible for periodically assessing study data according to an agreed upon schedule (as well as on an ad hoc basis) and making a recommendation to balcinrenone/dapagliflozin project team. The processes, roles and responsibilities will be described in the CCI [REDACTED] Charter.

CCI [REDACTED]

CCI [REDACTED]

CCI



A 6 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on www.astrazenecaclinicaltrials.com <http://www.clinicaltrials.gov> and <https://euclinicaltrials.eu/> as will the summary of the main study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to AstraZeneca or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- QTLs will be predefined in the IQRMP to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarised in the CSR.
- Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plan.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently

approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring Plan.

- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification as per the Monitoring Plan(s) to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention and Disposal Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the source data agreement and computerised data checklist for electronic source data.

A 9 Study and Site Start and Closure

The site study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened (ie, who signed consent) and will be the study start date.

AstraZeneca designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of AstraZeneca. Study sites will be closed upon study

completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by AstraZeneca or the investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, AstraZeneca's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, AstraZeneca shall promptly inform the investigators, the IRBs/IECs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to AstraZeneca before submission. This allows AstraZeneca to protect proprietary information and to provide comments.
- AstraZeneca will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, AstraZeneca will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B AEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of AEs

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of SAEs

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

AEs for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-SAE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

‘Life-threatening’ means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the medicinal product would result in the participant’s death. ‘Life-threatening’ does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of important medical events:

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When assessing causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the medicinal product.

- Time Course. Exposure to suspect drug. Has the participant received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host, or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as ‘not related’.

Causal relationship in cases where the DUS has deteriorated due to lack of effect should be classified as ‘no reasonable possibility’.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- **Was identified and** intercepted before the participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error

- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person

- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at the site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment, and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

All appropriately consented samples will be retained for maximum 15 years from last subject last visit.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures the participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented, and study site is notified.

C 3 International Air Transport Association Guidance Document 62nd edition

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

The International Air Transport Association (IATA) (<https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx>) classifies infectious substances into 3 categories: Category A, Category B, or Exempt.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.

Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- Are to be packed in accordance with UN 3373 and IATA 650

Exempt Substances are substances which do not contain infectious substances, or substances which are unlikely to cause disease in humans or animals, are not subject to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations.
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (<https://www.iata.org/contentassets/b08040a138dc4442a4f066e6fb99fe2a/dgr-62-en-pi650.pdf>).
- Biological samples transported in dry-ice require additional dangerous goods specification for the dry-ice content.

Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

D 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report potential Hy's Law cases and Hy's Law cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential Hy's Law criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of potential Hy's Law and Hy's Law events; this includes samples collected at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, potential Hy's Law criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible potential Hy's Law events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting potential Hy's Law criteria to agree whether Hy's Law criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The investigator is responsible for recording data pertaining to potential Hy's Law/Hy's Law cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

D 2 Definitions

Potential Hy's Law

Aspartate aminotransferase or ALT $\geq 3 \times \text{ULN}$ **together with** TBL $\geq 2 \times \text{ULN}$ at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law

Aspartate aminotransferase or ALT $\geq 3 \times \text{ULN}$ **together with** TBL $\geq 2 \times \text{ULN}$, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For potential Hy's Law and Hy's Law the elevation in transaminases must precede or be

coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

D 3 Identification of Potential Hy's Law Cases

In order to identify cases of potential Hy's Law it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- $ALT \geq 3 \times ULN$
- $AST \geq 3 \times ULN$
- $TBL \geq 2 \times ULN$

Central Laboratories Being Used:

When a participant meets any of the potential Hy's Law identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to AstraZeneca representative).

The investigator will also remain vigilant for any local laboratory reports where the potential Hy's Law identification criteria are met, where this is the case, the investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the investigator will without delay:

- Determine whether the participant meets potential Hy's Law criteria (Appendix [D 2](#) for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

D 4 Follow-up

D 4.1 Potential Hy's Law Criteria not met

If the participant does not meet potential Hy's Law criteria the investigator will:

- Inform the AstraZeneca representative that the participant has not met potential Hy's Law criteria.

- Perform follow-up on subsequent laboratory results according to the guidance provided in the protocol.

D 4.2 Potential Hy's Law Criteria met

If the participant does meet potential Hy's Law criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within one day of potential Hy's Law criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important Medical Event' and causality assessment 'yes/related' according to the protocol process for SAE reporting.
- For participants who met potential Hy's Law criteria prior to starting IMP, the investigator is not required to submit a potential Hy's Law SAE unless there is a significant change[#] in the participant's condition.
- The Study Clinical Lead will contact the investigator, to provide guidance, discuss, and agree an approach for the study participant's follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the investigator will:
 - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete follow-up SAE Form as required.
 - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Clinical Lead. This includes deciding which the tests available in the Hy's Law laboratory kit should be used.
 - Complete the 3 Liver eCRF Modules as information becomes available

[#]A '**significant**' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Clinical Lead if there is any uncertainty.

D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this appendix should be followed for all cases where potential Hy's Law criteria are met.

As soon as possible after the biochemistry abnormality is initially detected, the Study Clinical Lead will contact the investigator in order to review available data and agree on whether there is an alternative explanation for meeting potential Hy's Law criteria other than DILI caused by

the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date potential Hy's Law criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE: Update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term, causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
 - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
 - As there is no alternative explanation for the Hy's Law case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether the case meets the criteria for Hy's Law, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to protocol process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether Hy's Law criteria are still met. Update the previously submitted potential Hy's Law SAE report following protocol process for SAE reporting, according to the outcome

of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

D 6 Laboratory Tests

Hy's Law Laboratory Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA ^a IgG anti-HCV HCV RNA ^b IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG ^d anti-CMV IgG anti-HSV, and HSV 1/2 IgM testing or HSV PCR ^d IgM & IgG ^d anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) ^c
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

^a HBV DNA is only recommended when IgG anti-HBc is positive.

^b HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.

^c CD-transferrin and Transferrin are not available in China. Study teams should amend this accordingly.

^d HSV 1/2 IgM testing or HSV 1/2 PCR testing depending on region.

D 7 References

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Appendix E Country-specific Requirements

Table 7 Country-specific Requirements

Country	Applicable Local Requirement	CSP Section	CSP Local Adaptation
Austria	Participants requiring legal representation not permitted	Section 8.4 Appendix A	In Austria no participants requiring legal representation will be included in this clinical study.
	Pregnancy test during each visit	Section 1.3 Schedule of activities.	In Austria pregnancy test to be completed locally at each visit unless central laboratory test is planned.
Bulgaria	Home visits are not permitted	Not applicable (Home visits are not mandated in this study)	No CSP local adaptation required.

Appendix F Strong and Moderate Cytochrome P450 3A4 (CYP3A4) Inhibitors and Inducers

Strong or moderate CYP3A4 inhibitors or inducers are prohibited at least one week prior to randomisation and for the duration of the IMP treatment. This is applicable only if there is significant systemic exposure to the drug (for example oral or intravenous administration). Local treatment is allowed due to the negligible systemic exposure.

The following list (Table 8) is not intended to be exhaustive and a similar restriction will apply to other agents that are known to modulate CYP3A4 activity. Appropriate medical judgement is required. The investigator is to contact the AstraZeneca representative in case of questions.

Table 8 CYP3A4-interacting Medication That are Prohibited During the Study

Medication	Rationale
Boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole	Strong CYP3A4 inhibitors which may increase balcinrenone concentrations.
Apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	Strong CYP3A4 inducers which may decrease balcinrenone concentrations.
Aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil	Moderate CYP3A4 inhibitors which may increase balcinrenone concentrations.
Bosentan, efavirenz, etravirine, phenobarbital, primidone	Moderate CYP3A4 inducers which may decrease balcinrenone concentrations.

F 1 Reference

FDA Guidance Drugs that Interact with CYP Enzymes and Transporter Systems 2023
FDA guidance – FDA's Examples of Drugs that Interact with CYP Enzymes and Transporter Systems: CYP Enzyme- and Transporter System-Based Clinical Substrates, Inhibitors, or Inducers (content current as of 06 May 2023). Available at <https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems>. Accessed on 09 Jan 2024.

Appendix G List of Preferred Terms Defining the Adverse Events of Special Interest

The PTs are based on MedDRA English version 27.1

Hyperkalaemia

- Hyperkalaemia
- Blood potassium increased

Hypotension

- Hypotension
- Diastolic hypotension
- Orthostatic hypotension
- Dizziness
- Dizziness postural
- Presyncope
- Syncope

Renal events/AKI (based on narrow SMQ Acute renal failure, except for PTs marked with *)

- Acute kidney injury
- Acute phosphate nephropathy
- Anuria
- Azotaemia
- Blood creatinine increased*
- Continuous haemodiafiltration
- Creatinine renal clearance decreased*
- Dialysis
- Foetal renal impairment
- Glomerular filtration rate decreased*
- Haemodialysis
- Haemofiltration
- Neonatal anuria
- Nephropathy toxic
- Oliguria
- Peritoneal dialysis
- Prerenal failure
- Renal failure
- Renal failure neonatal
- Renal impairment
- Renal impairment neonatal
- Subacute kidney injury

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