The George Institute for Global Health

CAPTIVATE

CAPTIVATE

The Chronic kidney disease Adaptive Platform Trial Investigating Various Agents for Therapeutic Effect

The Chronic kidney disease Adaptive Platform Trial Investigating Various Agents for Therapeutic Effect (CAPTIVATE)

Mineralocorticoid Receptor Antagonist (MRA) Domain-Specific Appendix V2.0, 16 November 2023

Protocol Number: P01351

Name: Sradha Kotwal
Role: MRA DSA Chief Investigator
Signature: Sradha Kotwal Digitally signed by Sradha Kotwal Date: 2023.11.28 10:22:23 +11'00'

Name: Hiddo Lambers-Heerspink
Role: MRA DSA Chief Investigator
Signature: 29 Nov 2023

1 TABLE OF CONTENTS

2 ABBREVIATIONS

Abbreviation	Definition
ACEi	Angiotensin-Converting Enzyme inhibitor
AESI	Adverse Event of Special Interest
ARB	Angiotensin Receptor Blocker
BP	Blood Pressure
CKD	Chronic Kidney Disease
CSDSR	Core Statistical Design and Simulation Report
DSA	Domain-Specific Appendix
DSC	Domain-Specific Appendix Steering Committee
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
IUD	Intrauterine Device
K+	Potassium
MRA	Mineralocorticoid Receptor Antagonist
NHMRC	National Health and Medical Research Council
RASi	Renin-Angiotensin System Inhibitor
SGLT2i	Sodium-Glucose Cotransporter-2 Inhibitor
uACR	Urine Albumin-Creatine Ratio
uPCR	Urine Protein-Creatinine Ratio

3 INTRODUCTION

The Mineralocorticoid Receptor Antagonist (MRA) Domain-Specific Appendix (DSA) contains information on trial conduct that is specific to finerenone. This includes information that is specific to the domain, including any domain-specific eligibility criteria or procedures. All information provided in the DSA is in addition to, and never instead of, that provided in the Core Protocol. This DSA will test whether finerenone reduces the rate of eGFR decline, as measured by eGFR slope, compared to placebo in patients with chronic kidney disease (CKD) receiving standard of care therapy.

3.1 DSA Synopsis

DSA Title	CAPTIVATE MRA Domain-Specific Appendix (DSA)
DSA Chief Investigators	Sradha Kotwal; Hiddo Lambers-Heerspink
Intervention(s)	• Finerenone • Matched placebo
DSA-Specific Objectives	The objectives detailed in the Core Protocol apply to this DSA. In addition, the MRA DSA has a domain-specific secondary objective to determine the effect of the interventions on the time to the composite of ≥57% eGFR decline or kidney failure.
DSA-Specific Outcomes	The outcomes detailed in the Core Protocol apply to this DSA. In addition, the MRA DSA has a domain-specific secondary outcome of time to the composite of ≥57% eGFR decline or kidney failure.
DSA Inclusion Criteria	Potential participants must satisfy all of the inclusion criteria in the Core Protocol, and also satisfy the following: 1. Urine albumin-creatinine ratio (uACR) >200 mg/g or urine protein-creatinine ratio (uPCR) >300 mg/g from the most recent result in the previous 3 months. 2. On a stable standard of care treatment for CKD, including a SGLT2i unless there is a documented reason not to be using a SGLT2i, for 4 weeks before screening according to treating physician. 3. Treating physician believes finerenone is clinically appropriate for the participant. 4. Participant and treating physician are willing and able to perform MRA DSA procedures.
DSA Exclusion Criteria	Potential participants must have none of the exclusion criteria in the Core Protocol, and must have none of the following: 1. Recipient of kidney transplant 2. Hyperkalaemia (serum potassium ≥5.0 mmol/L) at time of screening 3. Current treatment with mineralocorticoid receptor antagonist (MRA), where the treating physician or patient is not willing to discontinue this medication 4. Known allergy, intolerance or contraindication to MRAs 5. Current treatment with strong CYP3A4 inhibitors 6. Systolic BP <110 mmHg or diastolic BP <55 mmHg without antihypertensive therapy at time of screening 7. Severe hepatic impairment (defined as Child-Pugh Class C) 8. Adrenal insufficiency 9. Currently pregnant or breast feeding, or intending to become pregnant
Sample Size	Maximum sample size of approximately 1000 participants.

Randomisation Principles	Equal randomisation to finerenone and matched placebo.

3.3 Administrative Information

3.3.1 DSA Funding

Funding sources for the CAPTIVATE trial are specified in the Core Protocol Section 3.2.2. This domain is funded via seed funding through The George Institute for Global Health and the Australian Government National Health and Medical Research Council (NHMRC) Clinical Trials and Cohort Studies grant (Grant Identification Number 2024079).

3.3.2 DSA Chief Investigators

MRA DSA Chief Investigators

Dr Sradha Kotwal, The George Institute for Global Health, Australia
Prof Hiddo Lambers-Heerspink, The George Institute for Global Health, Australia

3.3.3 DSA Steering Committee

A Mineralocorticoid Receptor Antagonist (MRA) DSA Steering Committee (DSC) has been convened to provide oversight of the MRA DSA.

4 BACKGROUND & RATIONALE

4.1 DSA-Specific Background

Mineralocorticoid receptor antagonists (MRAs) are a drug class that have been used in the management of resistant hypertension and heart failure for years. However, within the last decade, they have also been identified as an additional drug class that substantially reduces the risk of kidney failure and albuminuria. Large clinical trials have shown that MRAs, especially non-steroidal MRAs improve kidney and cardiovascular outcomes in individuals with CKD, with a reduction in cardiac and kidney risk of about 20% [1, 2].

The mineralocorticoid receptor is predominantly located in the aldosterone-sensitive distal nephron and regulates salt, potassium and water balance. For this reason, MRAs have been used for their diuretic and antihypertensive properties for decades. Clinical guidelines recommend MRA therapy for all patients with heart failure and a left ventricular ejection fraction of <40% to reduce hospitalisation and mortality rates[3]. The understanding of further direct and indirect renoprotective effects of MRAs continues to evolve and include the reduction of fibrosis, tubular injury, podocyte injury, vascular injury, inflammation and vasoconstriction[4].

The potential use of MRAs in CKD has sparked great interest, however the use of traditional steroidal MRAs (spironolactone, eplerenone) has previously been limited due to their risk of hyperkalaemia. To this end, novel non-steroidal MRAs (finenerone, esaxerenone) have recently been developed, which are more selective for the mineralocorticoid receptor compared to the steroidal agents, are less likely to cause hyperkalaemia and appear to be promising in CKD management [5]. Finerenone is highly selective for the mineralocorticoid receptor with no affinity for androgen, progesterone, oestrogen and glucocorticoid receptors and therefore does not cause sex hormone-related adverse events (e.g., gynecomastia) seen in the traditional steroidal MRAs (Finerenone Investigator's Brochure). Overall, the risk-benefit ratio of non-steroidal MRAs appear to be favourable compared to steroidal MRAs.

Finerenone has been approved by regulatory authorities worldwide including the US, Australia and Europe to treat CKD in patients with type 2 diabetes as long-term cardiac and renal protective benefits have been demonstrated in the FIDELIO-DKD[2] and FIGARO-DKD[6] clinical trials. Patients in the finerenone trials received angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) monotherapy as part of standard of care. KDIGO 2022 Clinical Practice Guidelines[7] recommend the use of finerenone in CKD patients with type 2 diabetes, an eGFR ≥25 mL/min/1.73 m^2,

normal serum potassium concentration and albuminuria (≥30 mg/g) despite maximum tolerated dose of RAS inhibitor (RASi). These finerenone trials were conducted prior to recent updates in guideline recommendations for the use of sodium-glucose cotransporter-2 inhibitors (SGLT2i) to reduce renal complications in CKD [8]. The baseline use of SGLT2i in the finerenone clinical trials was low (<10%), although this progressively increased during the course of the trials. Preclinical data suggest there are additive cardiorenal and proteinuria reduction benefits from the combination use of finerenone and SGLT2i [9], but clinical data are required to confirm this. The effects of finerenone on non-diabetic kidney disease and in combination with current standard of care including SGLT2i are also yet to be confirmed. The Finerenone In Non-Diabetic Chronic Kidney Disease (FIND-CKD) trial (ClinicalTrials.gov identifier (NCT number): NCT05047263) aims to address this knowledge gap.

Post hoc analyses of pooled data from the FIDELIO-DKD and FIGARO-DKD studies found finerenone reduced albuminuria regardless of baseline SGLT2i therapy (P interaction = 0.17) but resulted in a greater difference in chronic eGFR slope between treatment and placebo when combined with SGLT2i compared to monotherapy (−1.54 and −1.18 mL/min/1.73 m^2, respectively)[10]. Importantly, the incidence of hyperkalaemia was less with combination treatment compared with finerenone alone.

A small trial with the steroidal MRA, eplerenone, also showed a potential additive effect when used in combination with a SGLT2i. The ROTATE-3 study evaluated short-term outcomes of monotherapy and combination therapy with eplerenone and dapagliflozin, a SGLT2i, in 46 CKD patients with and without type 2 diabetes [11]. ROTATE-3 found that both eplerenone and dapagliflozin monotherapy reduced albuminuria after 4 weeks of therapy (33.7% and 19.6% reduction from baseline, respectively). The effects were more pronounced with combination therapy, which reduced albuminuria by 53% and suggests that the effects of both agents are independent and additive. ROTATE-3 also found a decline in eGFR in all 3 groups with a mean change of -3.3 mL/min/1.73m2 (95% CI, -5.6 to -1) with dapagliflozin, -5.6 mL/min/1.73m2 (95% CI, -7.6 to 3.2) with eplerenone and -6.9 mL/min/1.73m2 (95% CI, -9.2 to -4.6) with dapagliflozin-eplerenone therapy from baseline to week 4, which was reversible with a rise in eGFR 4 weeks following drug cessation (Figure 1). This acute decline in eGFR is a common feature of kidney protective drugs and during long-term treatment, has been associated with kidney protection [12].

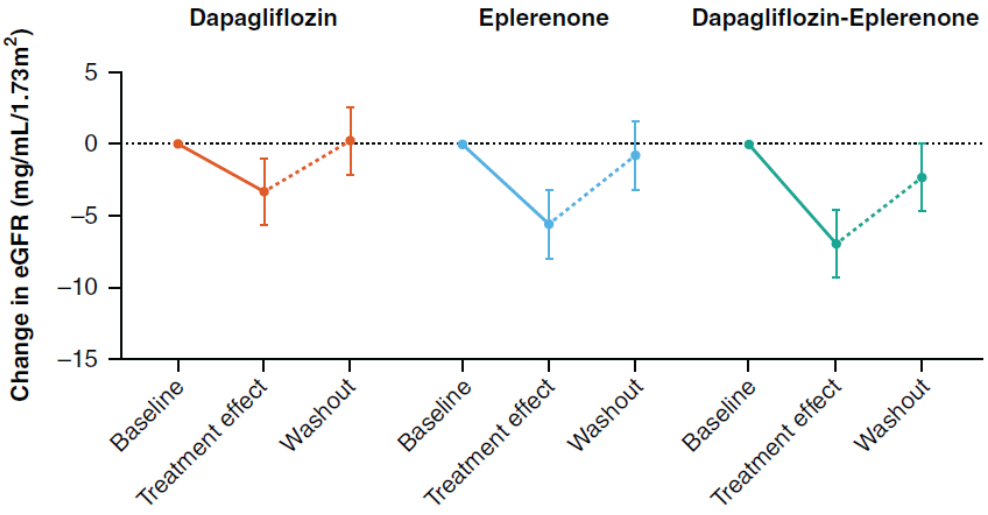

Figure 1: Change in eGFR from baseline during treatment with dapagliflozin, eplerenone, and dapagliflozin-eplerenone in ROTATE-3 study.

4.2 DSA-Specific Rationale

Clinical trials are required to confirm the potential additive cardiac and renoprotective effects of combined MRA and SGLT2i therapy. This is particularly important now that standard of care in CKD typically includes a SGLT2i. Results from the treatment of CKD in the ROTATE-3 trial [11] are promising for the combination use of MRA and SGLT2i. ROTATE-3 also showed that benefits extended to patients without type 2 diabetes. Concerns about hyperkalaemia from MRA are mitigated by data that show this risk may be reduced by the use of non-steroidal MRAs and in combination with a SGLT2i[13, 14]]. Due to the lower risk of hyperkalaemia, finerenone is approved for individuals with lower eGFR (≥25ml/min/1.73m^2) compared to the traditional steroidal MRAs (eplerenone eGFR cut off ≥30ml/min/1.73m^2) for people with heart failure, Eplerenone Australian Product Information, https://www.tga.gov.au/resources/artg/100162) thus increasing accessibility. A larger prospective trial in patients with CKD from any cause is required to confirm long-term efficacy and safety of combined selective non-steroidal MRA plus SGLT2i.

The MRA DSA of CAPTIVATE aims to evaluate if the selective non-steroidal MRA, finerenone, has beneficial effects in patients with CKD when used on top of standard of care treatment which now typically includes SGLT2i plus RASi. This study includes participants with CKD regardless of diabetes status. As additional domains are added to the CAPTIVATE trial, the effects of finerenone in combination with other promising therapeutic treatments for CKD will also be studied.

5 DSA-SPECIFIC OBJECTIVES

The objectives detailed in the Core Protocol apply to this DSA. In addition, the MRA DSA has a domain-specific secondary objective to determine the effect of the interventions on the time to the composite of ≥57% eGFR decline or kidney failure.

6 TRIAL DESIGN

6.1 DSA Eligibility Criteria

6.1.1 DSA Inclusion Criteria

Potential participants must satisfy all of the inclusion criteria in the Core Protocol, and also satisfy the following:

1. Urine albumin-creatinine ratio (uACR) >200 mg/g or urine protein-creatinine ratio (uPCR) >300 mg/g from the most recent result in the previous 3 months.
2. On a stable standard of care treatment for CKD, including a SGLT2i unless there is a documented reason not to be using a SGLT2i*, for 4 weeks before screening according to treating physician.
3. Treating physician believes finerenone is clinically appropriate for the participant.
4. Participant and treating physician are willing and able to perform MRA DSA procedures.

*Potential reasons for not using a SGLT2i could include intolerance (including allergy or absolute contraindication), cost or inaccessibility (including unavailability), participant refusal or physician decision.

6.1.2 DSA Exclusion Criteria

Potential participants must have none of the exclusion criteria in the Core Protocol, and must have none of the following:

1. Recipient of kidney transplant
2. Hyperkalaemia (serum potassium ≥5.0 mmol/L) at time of screening
3. Current treatment with MRA, where the treating physician or patient is not willing to discontinue this medication
4. Known allergy, intolerance or contraindication to MRAs

5. Current treatment with strong CYP3A4 inhibitors**
6. Systolic BP <110 mmHg or diastolic BP<55 mmHg without antihypertensive therapy at time of screening
7. Severe hepatic impairment (defined as Child-Pugh Class C)
8. Adrenal insufficiency
9. Currently pregnant or breast feeding, or intending to become pregnant

**Strong CYP3A4 inhibitors: For example, (oral) ketoconazole, itraconazole, ritonavir, clarithromycin

6.2 Interventions

Participants will be randomised to either finerenone or matched placebo. The dosage of the study medication is informed by the participant's kidney function and serum potassium levels (refer to Section 7.1.2). The first dose of the allocated study medication will be administered as soon as possible (within 7 days) after randomisation. Participants must continue to receive standard of care therapy as per local guideline recommendations during their participation in this DSA.

6.3 DSA-Specific Outcomes

The outcomes detailed in the Core Protocol apply to this DSA. In addition, the MRA DSA has a domain-specific secondary outcome that evaluates the time to the composite of ≥57% eGFR decline or kidney failure.

7 TRIAL CONDUCT

7.1 Study Intervention

Finerenone 10mg or 20mg tablets and matched placebo tablets will be used in this DSA. The Finerenone (BAY 94-8862) Investigator's Brochure contains detailed information about finerenone.

A summary of clinical guidance for the initiation, dosing and management of toxicities for the use of finerenone in the CAPTIVATE trial is presented in this section. Full clinical guidance for the use of finerenone in the trial is contained in the CAPTIVATE finerenone guidance document.

7.1.1 Supply, Labelling & Storage

Finerenone and matched placebo tablets will be manufactured and supplied by Bayer AG in 10mg and 20mg formulations. The tablets will be supplied by Bayer AG in bottles of 36 tablets for the trial.

Both finerenone and placebo tablets will be labelled, stored and distributed to study sites by a professional pharmaceutical packaging service, according to Good Manufacturing Practice guidelines. All study medication will be labelled in a double-blind format. Depot facilities in specific countries will be established as required. Depots will help to store and distribute study medication to local sites.

The study site is responsible for the secure storage of study medication at the site. The study medication must be kept in a locked area with restricted access and handled in accordance with the Sponsor's instructions. There are no special storage conditions required for the study medication.

Study medication will be administered from randomisation to Week 104. Study medication will be dispensed to participants at randomisation, and at the Week 4, Week 24, Week 52 and Week 78 study visits. If the finerenone dose is changed between 10mg and 20mg, the study medication will be dispensed in the new formulation as required throughout the study.

7.1.2 Dosage & Administration

Finerenone or placebo tablets will be administered orally with a full glass of water with or without food and should be taken at about the same time on each day of administration.

If a dose of the study medication is missed, it should be taken as soon as possible after it is noticed provided that it is on the same day. If this is not possible, the dose should be skipped and the next dose taken according to schedule. The participant should not take a double dose to make up for the missed dose.

Dosage

Kidney function and serum potassium must be taken into consideration when dosing finerenone (see Table 1). For the CAPTIVATE trial, initiation of finerenone is contraindicated in patients with an eGFR <25 mL/min/1.73m^2, serum potassium (K+) ≥5.0 mmol/L or severe hepatic insufficiency at the Screening Visit. Finerenone is dosed at either 10mg once daily or 20mg once daily as per Table 1.

4 weeks after initiation, recommencement or up-titration of finerenone, the finerenone dose may require adjusting based on eGFR and serum potassium as per Table 1. For participants with serum potassium >5.5 mmol/L at 4 weeks, finerenone may be suspended. Dietary and/or other interventions are to be implemented to lower serum potassium levels as per local practice. Blood tests should be repeated in 1 week's time to monitor potassium levels (or earlier if clinically indicated as per local guidelines). Consider recommencing finerenone at 10mg once daily once the serum potassium has stabilised to ≤5.0 mmol/L if appropriate as determined by the treating clinician.

Table 1: Finerenone dosage and dose adjustment*

Baseline eGFR (mL/min/1.73m^2)	Starting Dose	Dose at 4 weeks and thereafter Dependent on serum potassium levels (K+, mmol/L)$^{\alpha}$		
	K+ < 5.0	K+ < 5.0	K+ 5.0-5.5	K+ >5.5
≥ 60	20mg once daily	20mg once daily	20mg once daily	Suspend Restart at 10 mg once daily if serum potassium ≤5.0 mmol/L
25-59	10mg once daily	Increase the dose to 20mg once daily if eGFR decrease is ≤ 30% lower than the eGFR value at the previous visit	10mg once daily	Suspend Restart at 10 mg once daily if serum potassium ≤5.0 mmol/L

* CYP34A Inhibitors: If the participant is receiving strong CYP3A4 inhibitors (e.g. (oral) ketoconazole, itraconazole, ritonavir, or clarithromycin), finerenone should be withheld while the participant is receiving these medications. If the participant is receiving less potent CYP3A4 inhibitors (e.g. erythromycin, amiodarone, diltiazem, verapamil, or fluconazole), the serum potassium should be monitored especially during initiation of or changes to dosing of finerenone or the CYP3A4 inhibitor

$^{\alpha}$ Up-titration or maintenance of the starting dose at 4 weeks should only occur if the eGFR reduction is ≤ 30% lower than the baseline eGFR value. A reduction in eGFR of >30% is beyond the expected haemodynamic effects of finerenone.

Dose Adjustments

Finerenone may be titrated throughout the study. Finerenone may be up-titrated from 10mg to 20mg once daily at any study visit, including and after the Week 4 visit provided:

- Participant has been on a stable dose of finerenone for ≥4 weeks

- Serum potassium is <5.0 mmol/L
- eGFR decrease is ≤ 30% lower than the eGFR value at the previous visit.

Blood tests to monitor the serum potassium and eGFR should be performed 4 weeks after the initiation or re-start or up-titration of finerenone.

Finerenone may be down-titrated or suspended at any time during the study for safety reasons. In the case of hyperkalaemia, a repeat blood test for serum potassium should be performed within 1 week, or earlier if clinically indicated. If the repeat serum potassium is ≤5.0 mmol/L, finerenone can be resumed at the lower 10mg once daily dose.

Standard of care should be continued throughout the study.

Pharmacokinetic Considerations

Finerenone metabolism is primarily mediated via CYP3A4. Significant pharmacokinetic interactions may occur when finerenone is co-administered with drugs that inhibit the CYP3A4 enzyme. The concomitant use of finerenone with strong CYP3A4 inhibitors such as (oral) ketoconazole, itraconazole, ritonavir and clarithromycin is contraindicated. Cautious monitoring for adverse events such as hyperkalaemia is advised when less potent CYP3A4 inhibitors (erythromycin, amiodarone, diltiazem, verapamil, or fluconazole) are co-administered with finerenone.

7.1.3 Adherence to Treatment

Participants will be instructed to bring back any of their unused study medication at each study visit. Compliance will be assessed by tablet counts and details recorded in the electronic case report form (eCRF).

Tablets should be re-dispensed to the same participant after tablet counting if this is permitted by local regulations and if the dose has not changed. Participants should continue to use tablets from the previously dispensed bottle. Re-dispensing of unused study medication to the same participant must be in accordance with local procedures and policies. Strict hygiene measures must be enforced when handling the study medication.

Participants will remain on the randomised study medication without interruption. If study treatment is missed, or discontinued for any reason, relevant information should be documented within the participant's medical record and reported via the appropriate eCRF.

Participants who deviate from the dosing schedule for any reason will continue to be analysed according to intention-to-treat trial principles.

7.1.4 Accountability & Destruction

The Investigator or designee will keep accurate records of the quantities of the study medication received, dispensed, used, and returned by each participant. The study monitor will periodically check the supplies of study medications held by the investigator or pharmacist to verify accountability of all study medications used.

For the reasons of safety, institutional regulation, and storage capacity at sites, all used study medications during the course of the study, may be destroyed by investigational site staff according to local guidelines. Destruction should only occur following inspection by the study monitor, unless authorised in writing by the Regional Coordinating Centre. A complete accountability of study medication used by the participants must be available for verification by the study monitor. Similarly, at the conclusion of the DSA, any unused study medication may be destroyed locally following the final monitoring inspection.

Documentation of study medication destruction, listing a complete inventory of study medications destroyed, must be filed and be available for verification in the investigator site file.

7.1.5 Management of Toxicities & Treatment Modification

The adverse effects of finerenone are listed below by frequency and extracted from the Finerenone Investigator's Brochure.

- Very common (≥10%): Hyperkalaemia
- Common (≥1%): Hypotension, decreased glomerular filtration rate, hyponatraemia, hyperuricemia

If there is an adverse reaction, appropriate supportive care should be given at the discretion of the investigator. Full clinical guidance for managing adverse reactions, including hyperkalaemia, and treatment modifications is contained in the CAPTIVATE finerenone guidance document.

Overdose

No cases of adverse events associated with overdosage of finerenone in humans have been reported. The most likely manifestation of human overdosage would be anticipated to be hyperkalaemia.

There is no specific antidote; treatment is symptomatic and supportive. Finerenone cannot be removed by haemodialysis. If hyperkalaemia develops, standard treatment should be initiated.

7.1.6 Treatment Discontinuation Criteria

Study medication will be suspended or discontinued for any of the following reasons:

- Serum potassium >5.5mmol/L (see Table 1)
- Unacceptable toxicity as determined by the participant or Investigator.
- Occurrence of an exclusion criterion affecting participant safety, e.g. pregnancy
- Required use of a concomitant treatment that is not permitted.
- Participant chooses to cease study medication treatment or withdraws their consent to participate in the trial or the DSA.
- Investigator chooses to cease study medication treatment, where it is in the participant's best interest to do so.
- Non-compliance with the study protocol that, in the opinion of the Investigator or Sponsor, warrants withdrawal from treatment with the study medication.

Should the conditions that required study medication discontinuation no longer exist, finerenone or matched placebo should be re-started if it is clinically appropriate to do so. The date of and reasons for discontinuing treatment, as well as re-start date if applicable, will be documented in the participant's medical record and eCRF.

Regardless of whether participants resume the study medication or not, all participants should be followed up until the end of the study. Discontinuation of the trial intervention does not constitute participant withdrawal from the trial. Participants who discontinue the trial intervention for any reason will remain in the study and continue with the schedule of study visits to provide data for the intention to treat analysis.

7.1.7 Concomitant therapy

7.1.7.1 Contraindications

Concomitant use of finerenone with strong CYP3A4 inhibitors (e.g. itraconazole, (oral) ketoconazole, ritonavir and clarithromycin) is contraindicated. If these medications are required, the study medication (finerenone or matched placebo) must be temporarily discontinued. The study medication

can be restarted once these medications are stopped and have washed out or will no longer be required.

7.1.7.2 Concomitant use of substances that affect finerenone exposure

Concomitant use of finerenone with moderate CYP3A4 inhibitors (e.g., erythromycin and verapamil) and weak CYP3A4 inhibitors (e.g., amiodarone and fluvoxamine) is expected to increase finerenone exposure. Serum potassium may increase, and therefore, monitoring of serum potassium is recommended.

Concomitant intake of grapefruit or grapefruit juice is expected to increase the plasma concentration of finerenone and should be avoided. Grapefruit can inhibit CYP3A4.

Concomitant use of finerenone with strong inducers of CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, phenobarbitone, St John's Wort) or with efavirenz and other moderate CYP3A4 inducers should be avoided due to the risk of decreased finerenone efficacy.

7.1.7.3 Pharmacodynamic interactions

It is anticipated that medications that increase serum potassium will increase the risk of hyperkalaemia when used concomitantly with finerenone.

Concomitant use of finerenone with the following medications should be avoided:

- Potassium-sparing diuretics (e.g., amiloride, triamterene)
- Other mineralocorticoid receptor antagonists (MRAs) (e.g., eplerenone, esaxerenone, spironolactone, canrenone)

Finerenone should be used with caution and serum potassium monitored when taken concomitantly with the following medications:

- Potassium supplements
- Trimethoprim, or trimethoprim-sulfamethoxazole. Temporary discontinuation of finerenone may be necessary.

Refer to the reference Finerenone Investigator's Brochure for additional information about medications that must be used with caution.

7.1.8 Concomitant Care

Any care or medications required to maintain participant well-being may be used at the investigator's discretion unless the medication is listed in the Contraindications section (Section 7.1.7).

7.2 DSA-Specific Assessments

The Core Schedule of Assessments in the core protocol applies to the MRA DSA. Additional assessments required for the MRA DSA are detailed below.

7.2.1 Pregnancy Test

All women of child-bearing potential must have a pregnancy test (urine or serum) performed at the Screening Visit. Women of child-bearing potential are defined as pre-menopausal women or women less than 1 year after the last menstrual period. If there are exceptional circumstances that prevent participants from attending clinic visits, such as COVID-19 travel restrictions or natural disasters, a home pregnancy test can be performed. A negative pregnancy test is required for randomisation into the MRA DSA.

7.2.2 Blood Tests

To monitor the safety of finerenone, an additional blood test for serum creatinine and potassium is to be performed 4 weeks after the re-start or dose increase of the study medication. If the dose is reduced or suspended due to hyperkalaemia, a blood test 1 week after dose reduction or suspension to monitor serum potassium levels should be performed if clinically appropriate.

These additional blood tests do not necessarily require an unscheduled visit. Participants are to be given a blood test request form for the additional test at the study visit where the dose is changed. The Investigator must review the test results to monitor participant safety. The site is responsible for ensuring that the participant performs these additional blood tests.

7.2.3 Study Medication Dispensing

Study medication is dispensed at randomisation, Week 4, Week 24, Week 52 and Week 78 visits. If the study medication dosage is changed between 10mg and 20mg, medication with the new formulation will be dispensed as required. Changes in dose can occur at scheduled study visits, including at the Week 12 visit if required. If dose changes are required between study visits, an unscheduled visit should be performed to dispense the new 10mg or 20mg formulation.

Should a new formulation be dispensed, all study medication bottles with the old formulation must be returned by the participant. The participant must never have both 10mg and 20mg formulations in their possession at the same time. The minimises the risk of accidental overdosing or underdosing from administration of study medication from the 'wrong' bottle.

7.2.4 Study Medication Adherence

Tablets counts will be performed at the Week 4, Week 24, Week 52, Week 78 and Week 104 visits to assess study medication adherence. If the study medication dose is changed at the Week 12 visit or at an unscheduled visit, tablet counts will be performed on medication bottles with the old formulation that are returned by the participant. Tablet counts must also be performed at the Early Treatment Discontinuation Visit (ETDV) if the participant permanently discontinues study medication before the End of Treatment visit at week 104. Approximate tablet counts are acceptable.

7.2.5 Contraception

Women must be 1 year post-menopausal, surgically sterile or must agree to use highly effective contraception during their participation in the MRA DSA and for one week after the last dose of study medication with all male sexual partners. Highly effective methods of contraception include having a vasectomised partner, or one of the following: hormonal contraceptives which inhibit ovulation (oral, injectable, transdermal, intravaginal or implants), Intrauterine Device (IUD), Intrauterine Hormone-releasing System (e.g., Mirena), bilateral tubal occlusion, vasectomised partner or sexual abstinence (https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf?fbclid=IwAR3AY5Ha0ESDyqIBeUaYI9VTFWmx9bbt8NZ-80N-5ME6pkBb1UHvFsTwqlQ).

7.2.6 DSA-Specific Schedule of Assessments

For the MRA DSA, additional assessments that will be conducted on top of those described in the Core Protocol are detailed in Table 2.

Table 2: MRA DSA Schedule of Assessments

Assessment	Screening	Randomisation	Active Follow-Up								Early Treatment Discontinuation	Passive Follow-up
Week	**-4**	**0**	**4**	**12**	**24**	**52**	**78**	**104 (EOT)**	**108**	**Unscheduled visit**	**4w after early discontinuation (ETDV)**	**Every 5 years**
Window	**Day -1 to Day -31**	**-**	**± 1w**	**± 4w**	**± 4w**	**± 4w**	**± 4w**	**± 2w**	**± 2w**	**-**	**± 2w**	**± 3m**
Blood tests[1]			X							(X)		
Pregnancy test[2]	X											
Finerenone/matched placebo dispensing[3]		X	X	(X)	X	X	X			(X)		
Study medication adherence			X	(X)[4]	X	X	X	X		(X)[4]	X	

Abbreviations: EOT = End of Treatment, ETDV = Early Treatment Discontinuation Visit, m = month, w = week

[1] Blood tests may be required outside study visits if the study medication dose is changed. A serum potassium blood test is performed 1 week after dose reduction or treatment suspension due to hyperkalaemia. Serum creatinine and potassium blood tests are performed 4 weeks after study medication re-start or dose increase. These blood tests do not necessarily require an unscheduled visit. Participants are to be given a blood test request form for these tests at the study visit where the dose is changed.

[2] Urine or serum pregnancy test in women of child-bearing potential.

[3] Study medication is dispensed at randomisation and Week 4, 24, 52, and 78 visits. If the study medication dosage is changed between 10mg and 20mg, the new formulation will be dispensed at scheduled study visits, including at the Week 12 visit if required. If the dosage is reduced between study visits, an unscheduled visit is performed to dispense the new formulation.

[4] If the study medication dose is changed at the Week 12 visit or at an unscheduled visit, tablets counts are performed on medication bottles with the old formulation that are returned by the participant.

7.3 Blinding & Unblinding

Finerenone and matched placebo will be administered on a blinded basis. Participants, site personnel, investigators and trial statisticians will remain blinded to the treatment.

Refer to Core Protocol, Section 8.5 for further details about blinding and emergency unblinding.

7.4 Criteria for DSA Discontinuation

The MRA DSA will be discontinued for any of the following reasons:

- Active follow-up has ceased in all participants within the DSA, and the DSA analyses have been performed and reported.
- At the request of the Platform Oversight Committee or a regulatory authority.

8 SAFETY MANAGEMENT

There are specific events for the MRA DSA that require reporting. These are in addition to the safety reporting requirements detailed in the Core Protocol.

8.1 Adverse Events of Special Interest

There are no additional adverse events of special interest (AESI) specifically for the MRA DSA. Hyperkalaemia is an AESI in the Core protocol and is also of special interest for the MRA DSA.

8.2 Pregnancy

Participants who are pregnant, breast feeding, or intending to become pregnant are excluded from the MRA DSA. Since the MRA DSA has an exclusion criterion for pregnancy, pregnancies that occur whilst the participant is receiving the study medication must be reported as per the Core Protocol. In addition, the site investigator is to report pregnancies that occur up to one week after the last dose of the study medication within one working day of the site becoming aware of the event. The participant is to be followed during the entire course of the pregnancy to report parental, foetal and neonatal outcomes.

Pregnancies that occur in the partner of a participant receiving finerenone or matched placebo do not require reporting.

Since participants must immediately discontinue the study medication if pregnancy occurs, exposure to the study medication during lactation is not expected to occur.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Overview

The primary analysis population is all randomised participants, regardless of adherence to the intervention, who were concurrently randomised and eligible for the MRA domain. Data will be analysed according to intention-to-treat principles. Statistical analyses will be performed separately for each intervention.

The primary outcome is eGFR slope measured from randomisation through to week 108. The treatment effect of finerenone will be estimated using a Bayesian linear mixed model. Details of the statistical analyses and example operating characteristics for this domain can be found in the Core Statistical Design and Simulation Report (CSDSR).

9.2 Sample Size

The maximum sample size is 500 participants randomised to finerenone matched by 500 participants randomised to matched placebo. This sample size provides approximately 90% power to detect a 1.3 mL/min/1.73m2/year improvement in chronic eGFR slope. Details of the power calculation can be found in Section 4 of the CSDSR.

9.3 Randomisation Principles

Eligible participants will be randomised equally (1:1) between finerenone and matched placebo. Randomisation will be stratified within each site for the MRA DSA. A computer-generated randomisation schedule using randomly-permuted blocks will be used to maintain balance within each stratum.

9.4 Analyses

[redacted]

9.4.1 Primary Analysis Population

[redacted]

9.4.2 Primary Analysis

[redacted]

9.4.3 uACR Analysis

[redacted]

9.4.4 Interim Analysis

[redacted]

[redacted]

9.4.5 Interaction Effects

[redacted]

10 ETHICAL CONSIDERATIONS

Potential participants who are being treated with a MRA at the time of screening will be excluded from the MRA DSA unless the treating physician and patient are both willing to discontinue the MRA.

The pharmaceutical company Bayer AG is supplying the study medication free of cost. Bayer AG provided input into the dosage, administration and safety of the study medication, but otherwise has no role in the study design, data collection, data analysis or writing of study reports. Bayer AG will be provided with de-identified data from the MRA DSA. A pooled analysis of data from the MRA DSA and data from finerenone trials in CKD sponsored by Bayer AG, including FIND-CKD, FIDELIO-DKD and FIGARO-DKD, may be conducted.

11 REFERENCES

1. Pitt, B., et al., *Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes.* NEJM, 2021. **385**(24): p. 2252-2263.
2. Bakris, G.L., et al., *Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes.* N Engl J Med, 2020. **383**(23): p. 2219-2229.
3. Atherton, J.J., et al., *National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the management of heart failure 2018.* Med J Aust, 2018. **209**(8): p. 363-369.
4. Barrera-Chimal, J., S. Girerd, and F. Jaisser, *Mineralocorticoid receptor antagonists and kidney diseases: pathophysiological basis.* Kidney Int, 2019. **96**(2): p. 302-319.
5. Agarwal, R., et al., *Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine.* Eur Heart J, 2021. **42**(2): p. 152-161.
6. Pitt, B., et al., *Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes.* New England Journal of Medicine, 2021. **385**(24): p. 2252-2263.
7. *KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease.* Kidney Int, 2022. **102**(5s): p. S1-s127.
8. *KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease.* Kidney Int, 2020. **98**(4s): p. S1-s115.
9. Kolkhof, P., et al., *Effects of Finerenone Combined with Empagliflozin in a Model of Hypertension-Induced End-Organ Damage.* American Journal of Nephrology, 2021. **52**(8): p. 642-652.
10. Rossing, P., et al., *Finerenone in Patients With Chronic Kidney Disease and Type 2 Diabetes by Sodium-Glucose Cotransporter 2 Inhibitor Treatment: The FIDELITY Analysis.* Diabetes Care, 2022. **45**(12): p. 2991-2998.
11. Provenzano, M., et al., *Albuminuria-Lowering Effect of Dapagliflozin, Eplerenone, and Their Combination in Patients with Chronic Kidney Disease: A Randomized Crossover Clinical Trial.* Journal of the American Society of Nephrology, 2022. **33**(8): p. 1569-1580.
12. Oshima, M., et al., *Insights from CREDENCE trial indicate an acute drop in estimated glomerular filtration rate during treatment with canagliflozin with implications for clinical practice.* Kidney Int, 2021. **99**(4): p. 999-1009.
13. Provenzano, M., et al., *Albuminuria-Lowering Effect of Dapagliflozin, Eplerenone, and Their Combination in Patients with Chronic Kidney Disease: A Randomized Crossover Clinical Trial.* J Am Soc Nephrol, 2022. **33**(8): p. 1569-1580.
14. Bakris, G.L., et al., *A prespecified exploratory analysis from FIDELITY examined finerenone use and kidney outcomes in patients with chronic kidney disease and type 2 diabetes.* Kidney Int, 2023. **103**(1): p. 196-206.

12 DSA AMENDMENTS

The full history of modifications to this DSA is described in the table below;

Version & Date	Changes from Prior Version
v1.1, 20Jul2023	N/A
v2.0, 16Nov2023	Investigational product changed from 'eplerenone' to 'finerenone' throughout document. All protocol sections updated with information for finerenone.
	Section 9.4.5: Added statistical information about interaction effects between interventions.