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Title Page

Protocol Title: A multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of finerenone on morbidity and mortality in participants with heart failure (NYHA II-IV) and left ventricular ejection fraction ≥ 40% (LVEF ≥ 40%)

Amendment Number: Not applicable

Protocol Number: 20103

Compound Number: Finerenone / BAY 94-8862

Study Phase: 3

Short Title: Efficacy and safety of finerenone in participants with symptomatic heart failure and left ventricular ejection fraction ≥ 40% (LVEF ≥ 40%).

Acronym: **FINEARTS-HF** (**FIN**erenone trial to investigate **E**fficacy and s**A**fety superio**R** to placebo in pa**T**ient**S** with **H**eart **F**ailure)

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Regulatory Agency Identifier Number(s): EudraCT 2020-000306-29

Approval Date: 05 MAR 2020

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The Medical Monitor's name and contact information will be provided separately.

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of finerenone on morbidity and mortality in participants with heart failure (NYHA II-IV) and left ventricular ejection fraction ≥40% (LVEF ≥40%).

Short Title: Efficacy and safety of finerenone in participants with symptomatic heart failure and left ventricular ejection fraction ≥40% (LVEF ≥40%).

Rationale: Study 20103 will be the first large-scale, long-term outcome study investigating the efficacy and safety of the non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone on morbidity and mortality in participants with heart failure (NYHA II-IV) and LVEF ≥40%.

An inappropriate release of aldosterone contributes to target organ damage found in heart failure (HF), myocardial infarction, chronic renal failure, and hypertension. The extensive expression of the mineralocorticoid receptor (MR) in the cardiovascular (CV) and renal systems, including myocytes, endothelial cells, vascular smooth muscle cells, and kidney mesangial cells, provides further evidence for the role of aldosterone in CV and renal injury.

Blockade of the action of aldosterone and potentially other MR ligands such as cortisol has been demonstrated to be of benefit in HF (Pitt et al. 1999, Zannad et al. 2010). Results from a short-term Phase 2b study (ARTS-HF Study 14564) reported a trend towards improvement of mortality and CV morbidity with finerenone treatment in addition to standard therapy for HF (Filippatos et al. 2016); however, long-term conclusive outcome studies examining whether MRAs can prevent CV events are still lacking in this patient population. Study 20103 will be the first study to address these questions in this population.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
1. To demonstrate the superiority of finerenone to placebo in reducing the rate of the composite CV endpoint.	Composite primary endpoint: • Cardiovascular (CV) death and total (first and recurrent) heart failure (HF) events (hospitalizations for heart failure [HHF] or urgent HF visits) in HF patients (New York Heart Association [NYHA] class II–IV) and LVEF ≥40%.
Secondary	
2. To determine the superiority of finerenone to placebo for each secondary endpoint 3. To assess the safety and tolerability of finerenone	Secondary endpoints: • Change from baseline to Month 6, 9 and 12 in Total Symptom Score (TSS) of the KCCQ • Time to first occurrence of composite renal endpoint: sustained decrease in estimated glomerular filtration rate (eGFR) ≥40% relative to baseline over at least 4 weeks, or sustained eGFR decline <15ml/min/1.73m^2 or initiation of dialysis or renal transplantation. • Time to all-cause mortality

Overall Design: Multicenter, randomized, double-blind, parallel-group, placebo-controlled

Intervention Model: Parallel-group assignment.

Primary Purpose: Treatment.

Number of Arms: 2

Masking:

- Sponsor
- Participant
- Care provider
- Investigator
- Outcomes assessor

Number of Participants: Approximately 6900 participants will be screened to achieve approximately 5500 randomly assigned to study intervention.

Intervention Groups and Duration:

Recruitment is expected to last for approximately 24 months. Randomization will take place within 2 weeks of screening. Eligible participants will be randomized in a 1:1 ratio to receive once daily (OD) treatment with finerenone or placebo. Planned treatment duration is approximately 18 to 42 months until expected events are reported. For participants still taking study intervention when the end of study is reached, the post-treatment follow-up period will last for 30 (+5) days and will end upon completion of the post-treatment (PT) phone call.

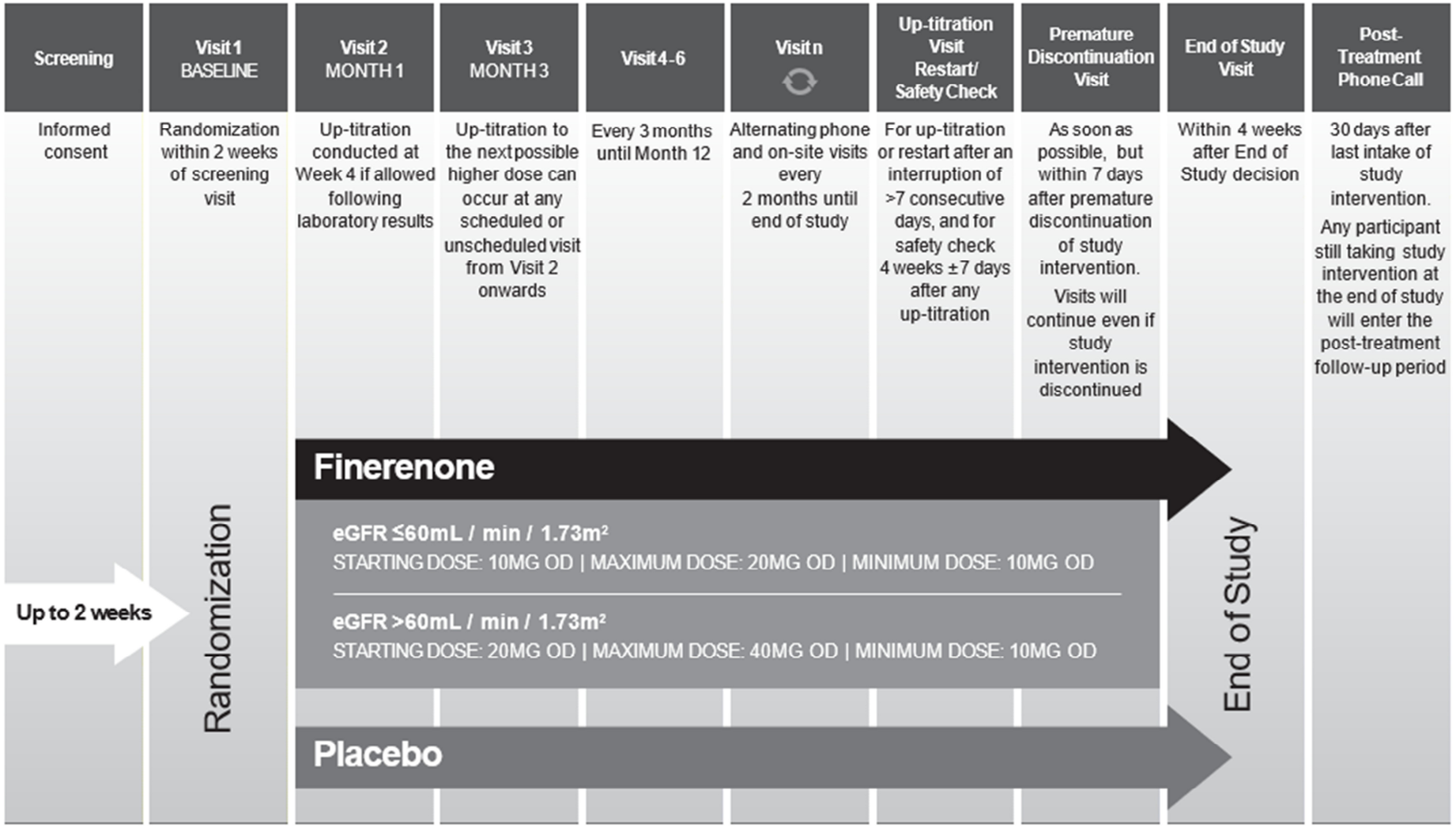
The starting dose will depend on the participant's eGFR level at the Baseline Visit: participants with an eGFR ≤60 mL/min/1.73m² will start with 10 mg OD (dose level 1) and have a maximum maintenance dose of 20 mg OD (dose level 2), whereas participants with an eGFR >60mL/min/1.73m² will start with 20 mg OD (dose level 2) and have a maximum maintenance dose of 40 mg OD (dose level 3). The minimum dose level is 10 mg for all participants. Medication intake is OD preferably in the morning.

Provided the participant's safety is not affected, and if considered appropriate by the investigator, the participant should be up-titrated to the next higher dose level ideally after 4 weeks of treatment, with the goal of keeping the participant on the maximum tolerated dose level for as long as possible. At any scheduled or unscheduled visit from Visit 2 (Month 1) onwards, up-titration to the next possible higher dose should be based on the level of serum/plasma potassium and eGFR. Participants will attend an additional safety visit 4 weeks ± 7 days after each up-titration. Down-titration or interruption of study intervention is allowed at any time during the study for safety reasons.

Concomitant therapy is best medical care to treat comorbidities at the investigator's discretion.

Data Monitoring Committee: Yes.

1.2 Schema


Screening
Visit 1 BASELINE
Visit 2 MONTH 1
Visit 3 MONTH 3
Visit 4-6
Visit n
Up-titration Visit Restart/ Safety Check
Premature Discontinuation Visit
End of Study Visit
Post-Treatment Phone Call
Informed consent
Randomization within 2 weeks of screening visit
Up-titration conducted at Week 4 if allowed following laboratory results
Up-titration to the next possible higher dose can occur at any scheduled or unscheduled visit from Visit 2 onwards
Every 3 months until Month 12
Alternating phone and on-site visits every 2 months until end of study
For up-titration or restart after an interruption of >7 consecutive days, and for safety check 4 weeks ±7 days after any up-titration
As soon as possible, but within 7 days after premature discontinuation of study intervention.
Visits will continue even if study intervention is discontinued
Within 4 weeks after End of Study decision
30 days after last intake of study intervention.
Any participant still taking study intervention at the end of study will enter the post-treatment follow-up period
Up to 2 weeks
Randomization
Finerenone
eGFR ≤60mL / min / 1.73m²
STARTING DOSE: 10MG OD | MAXIMUM DOSE: 20MG OD | MINIMUM DOSE: 10MG OD
eGFR >60mL / min / 1.73m²
STARTING DOSE: 20MG OD | MAXIMUM DOSE: 40MG OD | MINIMUM DOSE: 10MG OD
Placebo
End of Study

1.3 Schedule of Activities (SoA)

The schedule of activities (SoA) is displayed for the study as a whole in Figure 1–1 (‘*Main SoA*’) and for participants who prematurely discontinue the study, minimal assessments will need to be performed as outlined in Figure 1–2 (‘*Premature Discontinuation SoA*’).

Figure 1–1 Main SoA

Visit Number / Name	Screening [a]	Baseline [a] 1	2	3	4	5	6	7, 9, 11, 13, 15, 17, 19, 21 etc.[b]	8, 12, 16, 20 etc.	10, 14, 18 etc.	Up-titration, re-start and safety check [c]	PD Visit [d]	EOS Visit [e]	PT Visit [f]
Day (D) / Month (M)		D1	M1	M3	M6	M9	M12	M14 and every 4 months (i.e. M18, M22, M26, M30, M34, M38, M42 etc.)	M16 and every 8 months (i.e. M24, M32, M40 etc.)	M20 and every 8 months (i.e. M28, M36 etc.)				
Visit window (days)		-	±3	±3	±6	±6	±6	±7	±7	±7	±7			+5
On-site (O)/Tel. contact (☎)	O	O	O	O	O	O	O	☎	O	O	O	O	O	☎
Initiation procedures														
Informed consent	X													
Demographic data	X													
Substance use (alcohol & tobacco)		X												
Medical history	X													
NYHA class assessment	X	X	X	X	X	X	X	X	X	X		X	X	X
Prior and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
In- and exclusion criteria	X	X												
Clinical procedures/ assessments														
Weight	X	X	X	X	X	X	X		X	X	X	X	X	
Height	X													
Waist and hip circumference	X													
Vital signs [g]	X	X	X	X	X	X	X		X	X	X	X	X	
12-lead ECG (local)		X												
AE and endpoint assessment (renal endpoints require additional confirmed creatinine measurement; see Table 6–3 for details)		X	X	X	X	X	X	X	X	X	X	X	X	X

(main SoA continued below)

Figure 1–1 Main SoA

Visit Number / Name	Screening [a]	Baseline 1 [a]	2	3	4	5	6	7, 9, 11, 13, 15, 17, 19, 21 etc.[b]	8, 12, 16, 20 etc.	10, 14, 18 etc.	Up-titration, re-start and safety check [c]	PD Visit [d]	EOS Visit [e]	PT Visit [f]
Day (D) / Month (M)		D1	M1	M3	M6	M9	M12	M14 and every 4 months (i.e. M18, M22, M26, M30, M34, M38, M42 etc.)	M16 and every 8 months (i.e. M24, M32, M40 etc.)	M20 and every 8 months (i.e. M28, M36 etc.)				
Visit window (days)		-	±3	±3	±6	±6	±6	±7	±7	±7	±7			+5
On-site (O)/Tel. contact (☎)	O	O	O	O	O	O	O	☎	O	O	O	O	O	☎
(main SoA continued)														
Study intervention														
Randomization (IxRS)		X												
Dispense study intervention		X	X	X	X	X	X		X	X	X			
Provide and review the study contact card		X					X			X				
Administration of study intervention at study site		X		X										
Administration of study intervention before the visit			X		X	X	X		X	X				
Study intervention accountability			X	X	X	X	X		X	X	X	X	X	
Local/central laboratory														
Local laboratory [h] (potassium and creatinine [i])	X [j]	X [j]	X	X	X	X	X		X	X	X [k]	X	X	
Pregnancy test	X [L]	X [L]												
Central laboratory including urinalysis (see Table 10–1)		X [m]	X	X	X	X	X		X	X		X	X	
Exploratory biomarkers		X [m]		X			X						X	
Pharmacokinetics				X [n]			X [o]			X [o]				
Other study procedures														
KCCQ [q]		X			X	X	X		X			X	X	
EQ-5D-5L [q]		X			X	X	X		X			X	X	
PGIC [q]					X	X	X							
PGIS [q]		X			X	X	X							

Please note that footnotes to both SoAs can be found below Figure 1–2.

Figure 1–2 Premature Discontinuation SoA

Visit Number / Name		**2**	**3**	**4**	**5**	**6**	**7, 9, 11, 13, etc.[b]**	**8, 12, 16, 20 etc.**	**10, 14, 18 etc.**	**EOS Visit [e]**
Day (D) / Month (M)		**M1**	**M3**	**M6**	**M9**	**M12**	**M14 every 4 months (i.e. M18, M22 etc.)**	**M16 every 8 months (i.e. M24, M32, M40 etc.)**	**M20 every 8 months (i.e. M28, M36 etc.)**	
Visit window (days)		**±3**	**±3**	**±6**	**±6**	**±6**	**±7**	**±7**	**±7**	
On-site (O)/Tel. contact (☎)	**Premature discontinuation [p]**	**☎**	**O**	**O**	**☎**	**O**	**☎**	**O**	**O**	**O**
Central laboratory (eGFR)			X	X		X		X	X	X
AE and endpoint assessment (renal endpoints require additional confirmed creatinine measurement; see Table 6–3 for details)		X	X	X	X	X	X	X	X	X
Concomitant medication		X	X	X	X	X	X	X	X	X
KCCQ [q]				X		X		X		
EQ-5D-5L [q]				X		X		X		

Please note:

- 1 month corresponds to 30 days
- Study visits should occur as close as possible to the specified time points in the protocol, but time windows are permitted as specified in the SoA
- At any scheduled or unscheduled visit, the dose of study intervention may be increased to the next possible higher dose, based on serum/plasma potassium level analyzed in the local laboratory and provided the participant was already on a stable dose for 4 weeks ±7 days.

Abbreviations: AE = adverse event; D = Day; eGFR = estimated glomerular filtration rate; ECG = electrocardiogram; EOS = end-of-study; EQ-5D-5L = EuroQoL Group 5-dimension 5-level questionnaire; IxRS = interactive voice / web response system; med. = medication; KCCQ = Kansas City Cardiomyopathy Questionnaire; M = Month; NYHA = New York Heart Association; O = on-site; PGIC = Patient Global Impression of Change; PGIS = PGI of Severity; PD = premature discontinuation; PT = post-treatment; SoA = schedule of activities; Tel. = telephone

a Randomization has to occur within 2 weeks of the Screening Visit. If the Screening Visit and Visit 1 (Day 1, Baseline) are performed on the same day, procedures listed for both visits are to be performed only once.

b Study visits to be conducted as a clinic visit or a telephone contact visit. These visits will alternate at 4-monthly intervals from Month 12 onwards with participant contact being made every 2 months.

c This visit should be performed for safety check after any up-titration (4 weeks ±7days) and after restart of study intervention following an interruption for >7 consecutive days. An unscheduled safety visit should be performed within an adequate timeframe proposed by the investigator after any down-titration.

d The PD Visit should take place as soon as possible but within 7 days after premature discontinuation of study intervention. If the PD Visit cannot be performed within the timeframe specified, no PD Visit is required. All randomized participants will be followed until the study ends, even if they did not take study intervention or permanently discontinued study intervention.

e After the study site is notified of end of study decision, an EOS Visit should be scheduled as soon as possible (but within 4 weeks at the latest).

f For all participants still on treatment with study drug at the EOS Visit, the post-treatment (PT) telephone call (☎) has to be performed 30 days +5 days after the last intake of study drug.

g For vital sign collection, please adhere to instructions in Section 8.2.2.

h If BNP, NT-proBNP values (related to inclusion criteria) are not available in medical records, use values assessed by local laboratory.

i Creatinine will be used to calculate eGFR using CKD-EPI (Horio et al. 2010, Levey et al. 2009)

j If local laboratory data for potassium and eGFR are available within the last 24 hours, these may be used instead.

k Ensure that local laboratory data for potassium and eGFR are not older than 7 days.

L Female participants of childbearing potential must have a negative serum or urine pregnancy test at screening and baseline. Further serum or urine pregnancy tests should be performed in participants of childbearing potential as required by national/institutional regulations (e.g. at every visit). At any time during study participation, additional pregnancy testing should be performed upon suspicion of pregnancy.

m All procedures at Visit 1 are to be performed prior to randomization.

n One trough sample is to be collected at steady state before study intervention intake; study intervention is to be administered at the study site at this visit.

o Sample to be taken at any time during the visit after study intervention intake at home .

p The procedures/assessments to be performed at the PD Visit are listed in the main SoA (Figure 1–1). After completing the PD Visit, all subsequent visits are to be performed according to the Premature Discontinuation SoA (Figure 1–2). Any visits performed prior to the PD Visit do not need to be repeated (e.g. if PD is at Visit 5, there is no need to repeat previous visits).

q Questionnaires are to be completed by the participants before conducting any study procedure. See also Sections 8.1.1, 8.1.2 and 8.1.3 for details.

2. Introduction

Heart failure (HF) is usually a chronic progressive disease characterized by intermittent acute exacerbations. The underlying cause is usually a reduction in the ability of the heart to contract (systole) and/or fill (diastole) effectively.

HF is a leading cause of CV morbidity and mortality (Chen et al. 2011). Approximately 1-2% of the adult population in developed countries has HF, with the prevalence rising to ≥10% among persons 70 years of age or older (Mosterd and Hoes 2007). Projections in the US show that the prevalence of HF will increase by 46% from 2012 to 2030, resulting in >8 million people with HF (1 in every 33) in the US (Heidenreich et al. 2013). Similar results were found in selected western European countries (Danielsen et al. 2017).

Epidemiological studies have reported that about 50% of patients with HF have a relatively normal or slightly reduced left ventricular ejection fraction (LVEF), in the range of 40% and above, also referred to as HF with preserved ejection fraction (HFpEF) (Fonarow et al. 2007, Hogg et al. 2004, Owan et al. 2006, Swedberg et al. 1999, Yancy et al. 2006).

HFpEF is caused by a complex interplay of multiple impairments in ventricular diastolic and systolic reserve function, heart rate reserve and rhythm, atrial dysfunction, stiffening of the ventricles and vasculature, metabolic derangements, coronary microvascular dysfunction with impaired vasodilatation, pulmonary hypertension, endothelial dysfunction, and abnormalities in the periphery, including skeletal muscle (Borlaug 2014).

The ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure from 2016 identified patients with LVEF that ranges from 40 to 49% as a separate group and introduced a new term '*HF with mid-range ejection fraction (HFmrEF)*'.

When compared with HFrEF patients, patients with HFpEF are predominantly elderly, more women are affected and occurrence of comorbidities such as arterial hypertension and atrial fibrillation are higher in the HFpEF population whereas the occurrence of coronary artery disease was less likely (Bhatia et al. 2006, Fonarow et al. 2007, Martinez-Selles et al. 2012, Owan et al. 2006, Vaduganathan et al. 2016, Yancy et al. 2006).

As the population ages, the prevalence of diabetes mellitus, obesity and hypertension increases, the substrate for developing HF, in particular HFpEF, and its incidence will therefore increase dramatically in the coming decades (Owan et al. 2006). With the increased longevity in western societies, the enormous public-health problem of HFpEF will continue to grow. In this context, data from Get With The Guidelines–Heart Failure (GWTG-HF), a very large, nationwide study of HF hospitalization in the US (n >110,000) showed that the proportion of patients hospitalized with HF who had HFpEF increased from 33% in 2005 to 39% in 2010. Within the same time interval, the proportion of HHF due to HFrEF decreased from 52% to 47% (Steinberg et al. 2012).

HHF strongly predicts a poor prognosis: in patients with HFpEF the rates of mortality and re-admission at 60 to 90 days after discharge are as high as 9.5% and 29.2%, respectively and comparable as to the rates in HFrEF, being 9.8% and 29.9%, respectively. In hospital mortality was lower in HFpEF patients although the difference was small (Fonarow et al. 2007, Owan et al. 2006). HHF is the predominant cause of hospitalization in HFpEF patients representing a potential target in order to modify prognosis and quality of life.

To date, international guidelines acknowledge a lack of evidence in the management of HFpEF patients, as no treatment has yet been shown to reduce morbidity and mortality in

patients with HFpEF. Therefore management is limited to guideline-based optimal treatment of comorbidities as arterial hypertension, coronary artery disease and atrial fibrillation; diuretics are recommended in order to alleviate congestion symptoms. According to the ESC guidelines, management recommendations for patients with HFmrEF are the same as to patients with HFpEF (Ponikowski et al. 2016, Yancy et al. 2006). The ACC/AHA focused update of the guidelines in 2017 has included a class IIb recommendation for the use of aldosterone receptor antagonist in patients with stage C heart failure and LVEF ≥45%, elevated B-type natriuretic peptide (BNP) levels or HF admission within 1 year, eGFR >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L (Yancy et al. 2017).

A series of studies in different CV cell types demonstrated that MR ablation improves cardiac remodeling in experimental models of heart failure providing evidence that aldosterone directly mediates cardiac hypertrophy, fibrosis and inflammation via MR in the CV system (Fraccarollo et al. 2011, Lother and Hein 2016). In particular, MR in vascular cells appears to be crucially involved in the translation of CV risk factors such as obesity, diabetes mellitus or age into cardiac disease. Following the hypothesis that those risk factors are closely associated with vascular inflammation as a key driver for diastolic dysfunction, these findings suggest a potentially beneficial role for MR antagonists in HFpEF.

Spironolactone has been shown to reduce myocardial fibrosis/cardiac extracellular matrix and to improve arterial stiffness in animal models (Lacolley et al. 2001). In line with the data from pre-clinical studies, a meta-analysis of 11 randomized trials showed that administration of an MRA was associated with an improvement in diastolic function assessed by echocardiography, as well as with a reduction in the concentration of circulating cardiac biomarkers reflecting the collagen turnover associated with myocardial fibrosis (Pandey et al. 2015).

Since activation of the MR by aldosterone is known to promote arterial hypertension, endothelial dysfunction, left ventricular hypertrophy, and progressive vascular, renal, and myocardial fibrosis, all of which may contribute to the development of HFpEF, the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial sought to test the value of spironolactone as a treatment for HFpEF (Desai et al. 2011).

In this randomized, double-blind trial, 3445 patients with symptomatic heart failure and a left ventricular ejection fraction of 45% or more were assigned to receive either spironolactone (15 to 45 mg daily) or placebo. The randomization was stratified according to whether the patient met the criterion for previous HHF within the last 12 months or natriuretic peptide (NP) elevation within 60 days prior to randomization.

Treatment with spironolactone did not significantly reduce the primary composite endpoint which was death from CV causes, aborted cardiac arrest, or HHF (Pitt et al. 2014b).

However, there was a beneficial effect of spironolactone observed in the stratum of patients enrolled on the basis of elevated baseline B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. Furthermore, post hoc analysis revealed marked regional differences in incidence rates, baseline clinical profiles, adverse events, and compliance with study therapies. A ≈4-fold lower incidence rate in the composite endpoint was identified between the 1678 patients randomized from Russia and Republic of Georgia compared with the 1767 enrolled from the United States, Canada, Brazil, and Argentina (the Americas). Also, the proportion of patients enrolled on the basis of elevated natriuretic peptide levels versus previous hospitalization for HF was higher in the Americas than in patients from Russia and Georgia. In the Americas region, spironolactone reduced the incidence of the

primary endpoint compared to placebo. In addition, treatment with spironolactone in patients being enrolled from the Americas was associated with more frequent hyperkalemia, elevations in creatinine, reductions in blood pressure, and less hypokalemia (Pfeffer et al. 2015).

Analysis of the TOPCAT results in the Americas led to the class IIb recommendation added in 2017 to the ACC/AHA guidelines (Yancy et al. 2017) and gives reason to hope that targeting the MR could result in improved clinical outcome in patients with HFpEF. TOPCAT also prompted further investigation in 2 additional global Phase 3 randomized, open label clinical trials (ClinicalTrials.gov NCT02901184; EudraCT #2017-000697-11) with planned total enrollment of 4500 participants evaluating spironolactone in HFpEF.

Molecular pharmacological considerations suggest that the balance between the interstitial, anti-remodeling effects, and the renal epithelial, natriuretic, and antikaliuretic effects of mineralocorticoid receptor (MR) blockade can be modulated by the molecular structure of the pharmacological agent (Kolkhof and Borden 2012). The 3 currently marketed MRAs, spironolactone, canrenone, and eplerenone, have a steroidal chemical structure and are thus similar to the natural ligands of the MR receptor, aldosterone, and cortisol. Consequently, the similar structural and physicochemical properties of the steroidal MRAs determine the resulting pharmacological action, not only by their mode of binding to the MR, but also by their transport and distribution into different tissues and recruitment or blockade of tissue selective and ligand-specific co-factors (Kolkhof and Borden 2012).

Finerenone (BAY 94-8862) is an oral, selective and potent non-steroidal MRA of human MR in functional cellular transactivation assays combining *in vitro* spironolactone's potency with eplerenone's selectivity (Kolkhof and Borden 2012).

In animal models, finerenone reduced cardiac and renal hypertrophy, plasma prohormone of BNP and proteinuria more efficiently than in those treated with the steroidal MRA eplerenone, when comparing equi-natriuretic doses. Finerenone's tissue distribution pattern in rats was found to differ from the steroidal MRAs, i.e. spironolactone and eplerenone, which showed a higher accumulation of the drug equivalent concentration in kidney than in heart tissue, in contrast to finerenone which was found to be equally distributed in both the kidney and heart tissue (Kolkhof et al. 2014). Steroidal MRAs are known to interfere with the steroid hormone receptor, which can cause sexual side effects such as gynecomastia in men. However, finerenone is a non-steroidal and selective MRA *in vitro*, without any detectable affinity for the related androgen receptor; sexual side effects are therefore not expected to occur with finerenone at therapeutic dose levels.

In the safety and tolerability Phase 2 ARTS study (Pitt et al. 2013) finerenone in daily doses ranging from 2.5 to 10 mg was tested in comparison to placebo and spironolactone (25-50mg) in patients with HFrEF and mild to moderate kidney disfunction. Results showed trends towards greater reduction in NT-proBNP levels with finerenone 10mg compared with spironolactone, whereas increases in serum potassium were statistically significantly lower in finerenone arms compared to spironolactone. Moreover eGFR decline was smaller and incidence of worsening renal function was lower in all finerenone arms compared to spironolactone. Adverse events were reported in 79.4% of patients in the spironolactone arm and 53.1% in the highest dose finerenone arm which was comparable with the placebo group rates (50.8%).

In the dose finding Phase 2b ARTS-HF study in patients with worsening HFrEF and T2D and/or chronic kidney disease (CKD) (Filippatos et al. 2016) finerenone showed a decrease in

NT-proBNP >30% in similar proportion of patients to that of eplerenone. However, finerenone starting at the dose of 5-15mg OD was observed to reduce CV hospitalization and death from any cause to a greater extent compared to eplerenone, whereas the finerenone dose of 10-20 mg was associated with the lowest rates of the composite clinical endpoint. Rates of hyperkalaemia defined as potassium ≥ 5.6 mmol/L any time post baseline in the finerenone dose of 10-20mg (3.6%) were comparable to those in the eplerenone arm (4.7%).

Details of the results of the clinical and non-clinical development studies conducted with finerenone can be found in the Investigator Brochure.

2.1 Study Rationale

Study 20103 will be the first large-scale, long-term outcome study investigating the efficacy and safety of the non-steroidal MRA finerenone on morbidity and mortality in participants with heart failure (NYHA II-IV) and LVEF ≥ 40%, in comparison to placebo and in addition to standard-of-care therapy for congestion and comorbidities. As there is currently no approved therapy for heart failure with mid-range on preserved ejection fraction, placebo treatment was selected as comparator for this trial. Secondary endpoints will include change from baseline to Month 6, 9 and 12 in TSS of the KCCQ; time to first occurrence of composite renal endpoint: sustained decrease in estimated glomerular filtration rate (eGFR) ≥40% relative to baseline over at least 4 weeks, or sustained eGFR decline <15ml/min/1.73m^2 or initiation of dialysis or renal transplantation; time to all-cause mortality; and the safety and tolerability of finerenone.

An inappropriate release of aldosterone contributes to target organ damage found in heart failure, myocardial infarction, chronic renal failure, and hypertension. The extensive expression of the MR in the CV and renal systems, including the heart, endothelial cells, vascular smooth muscle cells, and kidney mesangial cells, provides further evidence for the role of aldosterone in CV and renal injury.

Blockade of the action of aldosterone and potentially other MR ligands such as cortisol has been demonstrated to be of benefit in HF. Results from a short-term Phase 2b study (ARTS-HF Study 14564) suggest that treatment with finerenone in addition to standard therapy for HF improves mortality and CV morbidity outcomes; however, long-term conclusive outcome studies examining whether non-steroidal MRAs can prevent CV events are still lacking. Study 20103 will be the first study to address these questions in this population.

Finerenone also has the potential to address the unmet medical need in patients with type 2 diabetes (T2D) and clinical diagnosis of CKD. The Phase 3 program with finerenone in patients with T2D and clinical diagnosis of CKD encompasses 2 placebo-controlled, large-scale, long-term outcome trials: Study 16244 examines whether finerenone can slow the progression of kidney disease and Study 17530 which is examining the effects of finerenone on CV outcomes. Both Phase 3 studies have enrolled over 13,000 participants since 2015 and are ongoing at the time of writing this protocol.

2.2 Background

Patients with HF exhibit an over activation of the renin-angiotensin-aldosterone system (RAAS) and the inappropriate release of aldosterone contributes to target organ damage, myocardial infarction, chronic renal failure, and hypertension. The extensive expression of the MR in the CV and renal systems, including myocytes, endothelial cells, vascular smooth muscle cells, and kidney mesangial cells, provides further evidence for the role of aldosterone in CV and renal injury.

Blockade of the action of aldosterone and potentially other MR ligands such as cortisol has been demonstrated to be of benefit in HF. Finerenone is a highly selective and potent non-steroidal mineralocorticoid receptor antagonist in development for treatment of chronic kidney disease in T2D patients as well as in HF.

A detailed description of the chemistry, pharmacology, efficacy, and safety of finerenone is provided in the Investigator's Brochure.

2.3 Benefit/Risk Assessment

In this study participants with heart failure (NYHA class II-IV) after recent HF decompensation and/or with elevated natriuretic peptides (BNP or NT-proBNP), will be given oral doses of finerenone once daily 10, 20 and 40 mg, depending on baseline eGFR, or placebo, in addition to standard-of-care therapies for congestion and comorbidities (i.e. RAAS inhibitors, beta-blockers, diuretics).

The eligibility criteria for this study 20103 have been chosen to adequately define a study population at high risk for worsening heart failure events , while excluding participants who may potentially be exposed to particular risks after study intervention administration or might benefit for intervention not included in the trial (i.e. amyloidosis, planed heart surgery).

Due to finerenone's mode of action, hyperkalemia is an important identified risk. However, in ARTS-HF (study 14564) the incidence of hyperkalemia was comparable between finerenone and eplerenone; and in ARTS (study 14563), all doses of finerenone resulted in significantly smaller serum potassium increase compared with spironolactone.

Worsening of renal function has been shown to occur with the steroidal MRAs, i.e. spironolactone and eplerenone (Rossignol et al. 2012). However, acute reductions in estimated glomerular filtration rate (eGFR) within the first 3 months upon starting RAAS blocking agents i.e. angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) or MRAs, in patients with CHF and/or CKD (Bakris and Weir 2000, Holtkamp et al. 2011) are postulated to reflect a hemodynamic response leading to reduced intraglomerular pressure, rather than therapy-induced damage to functioning nephrons (i.e. worsening of renal function). These changes are typically reversible on treatment withdrawal, and are associated with an attenuation of the long-term decline in eGFR (Heerspink et al. 2011).

In ARTS-HF (study 14564), the incidence of a relative decrease in eGFR of ≥30% from baseline was comparable between most of the finerenone dose groups (finerenone 2.5-5 mg n=8/119 (6.7%), finerenone 5-10 mg n=9/118 (7.6%), 7.5-15 mg n= 6/119 (5%), finerenone 10-20 mg n=7/130 (5.4%) and finerenone 15-20 mg n=15/120 (12.5%) except 15-20 mg OD) and the eplerenone (n=13/143 (9.1%) group (Filippatos et al. 2016) in supplementary material Table 10. In ARTS (study 14563), all doses of finerenone resulted in smaller eGFR decreases compared with spironolactone.

Potassium level and renal function will be closely monitored during treatment in this study (20103). In addition, patients will be included in this study only if serum/plasma potassium is ≤5.0 mmol/L. To minimize safety risks to the patient, starting doses of study medication will be chosen according to baseline renal function, and subsequent dose up-titration will be performed on the basis of measured potassium and eGFR values. Stopping rules for temporary and permanent discontinuation or dose reduction of study intervention based on potassium values will minimize the risk of hyperkalemia. At any time during the study, the investigator has the option to also down-titrate the study intervention, depending on serum potassium.

The high risk for CV mortality and morbidity in the population of this study (20103), taken together with the improved clinical outcomes seen with finerenone 10-20 mg OD compared with eplerenone in ARTS-HF (study 14564), indicate a positive risk-benefit assessment supporting the participation of participants in this study.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of finerenone may be found in the current Investigator's Brochure.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To demonstrate the superiority of finerenone to placebo in reducing the rate of the composite CV endpoint.	Composite primary endpoint: • Cardiovascular (CV) death and total (first and recurrent) HF events (HHF or urgent HF visit) in HF patients (New York Heart Association [NYHA] class II–IV) and LVEF ≥40%.
Secondary	
To determine superiority of finerenone to placebo for each secondary endpoint To assess the safety and tolerability of finerenone	Secondary endpoints: • Change from baseline to Month 6, 9 and 12 in Total Symptom Score (TSS) of the KCCQ • Time to first occurrence of composite renal endpoint: sustained decrease in estimated glomerular filtration rate (eGFR) ≥40% relative to baseline over at least 4 weeks, or sustained eGFR decline <15ml/min/1.73m^2 or initiation of dialysis or renal transplantation. • Time to all-cause mortality
Exploratory	
	Exploratory endpoints: • Time to first CV hospitalization • Time to first all-cause hospitalization • Total number of CV hospitalizations • Total number of all-cause hospitalizations • Time to first occurrence of the following composite endpoint: CV death or non-fatal CV event (i.e. non-fatal myocardial infarction, non-fatal stroke, or HHF) • Change in eGFR from baseline • Days alive and out of hospital • Time to new onset of atrial fibrillation • Change in health-related quality of life summary scores from baseline measured by the KCCQ and EQ-5D-5L • Change from baseline in NYHA class

An **urgent HF visit** is defined as an urgent, unscheduled presentation with signs and/or symptoms of an acute HF decompensation requiring prompt medical attention and intensification of the existing HF treatment or initiation of a new HF treatment (Hicks et al. 2018). Further details and definitions will be provided in the Outcome/Endpoint Manual and Clinical Event Committee (CEC) Charter.

According to the addendum to International Council on Harmonisation (ICH) E9 (ICH_E9 (R1) 2019), the 5 attributes of the primary estimand are as follows:

a) Population:
As described by inclusion/exclusion criteria given in Section 5

b) Variable:
Number of unfavorable events including CV death and total (first and recurrent) HHF

c) Treatment condition:
Finerenone vs. placebo

d) Intercurrent events:
There are 3 important intercurrent events to consider: treatment discontinuation, CV death and non-CV death. For treatment discontinuation, a treatment policy strategy will be applied, i.e. patients will be followed up for events after discontinuing treatment and events and follow-up time after discontinuation of treatment will be included in the analysis. CV death will be counted as both an outcome event as well as a censoring event, so that a combination of a composite and a while-alive strategy is used. Non-CV death is assumed to be a censoring event, since the treatment is not assumed to have an effect on these events and interest lies in the treatment effect on composite events while patients are alive

e) Population-level summary:
Ratio of exposure-weighted composite event rates between finerenone and placebo. Exposure-weighted refers to patients being weighted according to their follow-up time in determining the rate.

4. Study Design

4.1 Overall Design

Study 20103 is a randomized, double-blind, parallel-group, placebo-controlled, multicenter, event-driven Phase 3 study with independently adjudicated clinical outcome assessments. The overall study design is displayed as the schema in Section 1.2.

This study will be conducted in patients with HF and LVEF ≥40%.

Participants will be randomized in a 1:1 ratio to either finerenone or placebo. The study is designed to be able to show an effect on the primary endpoint with a power of 90% at an alpha level of 5%. It is anticipated that 5500 participants will be randomized and approximately 6900 will be screened (screening failure rate of approximately 20%). A total of approximately 2375 total (first and recurrent) primary composite events are targeted.

The anticipated duration of the study will be approximately 42 months, with a recruitment period of 24 months. However, as an event-driven study, the actual length of the study will depend on the observed event rates, the participant recruitment rate, and the length of the recruitment period.

Enrolment in the trial may be capped based on the proportion of patients in certain LVEF categories, in each NYHA class, with/without atrial fibrillation, and by geographic region, among other variables, to ensure recruitment of a representative study population.

The randomization will be stratified by country/region and LVEF (<60%, ≥60%). Additional details will be described in the Statistical Analysis Plan (SAP).

Data from this study will be reviewed for efficacy and safety on an ongoing basis by an independent Data Monitoring Committee (DMC). A detailed plan for these assessments will be provided in the DMC Charter.

A CEC blinded to study treatment assignment will adjudicate all events that could potentially fulfill the criteria for the primary and some of the secondary endpoints during the study. The CEC Charter will describe the roles and responsibilities of the CEC and define the events to be adjudicated and the manner in which they will be adjudicated.

The SoA in Section 1.3 summarizes the schedule of procedures.

This study will be event-driven, and all randomized participants will remain in the study until either (1) an instruction is received from the sponsor after the targeted number of primary efficacy events has occurred, or (2) the study is terminated early at the recommendation of the DMC. Therefore, all participants, including those who have stopped taking study intervention, should be asked to attend all the protocol-specified study visits in order to perform all assessments as stipulated in the main SoA (Figure 1–1); for participants who permanently discontinued study intervention, minimal assessments (e.g. central lab for eGFR) will need to be performed as outlined in the Premature Discontinuation SoA (Figure 1–2). If a participant is unable to attend a study visit, every effort should be made to contact the participant by telephone or other means (by checking medical and public records) to determine if any endpoints were reached at the time the study visits were scheduled for the remaining duration of the study. All attempts to retrieve information about the participant should be documented in the participant's records.

Screening

After providing written informed consent, a Screening Visit to confirm the participant's eligibility will take place prior to randomization. The Screening Visit may take place on the same day as randomization (Visit 1). Local laboratories will be used to perform the eligibility assessments (potassium, creatinine/calculated eGFR). NT-proBNP or BNP levels will be evaluated as per medical records or collected locally to check eligibility. Please note the 2 distinct thresholds for NT-proBNP or BNP regarding eligibility (see inclusion criterion 6 in Section 5.1).

The higher threshold for NT-proBNP or BNP should be used for patients with prior history of atrial fibrillation or in case the cardiac rhythm is unknown. If a participant is hospitalized for HF, screening procedures and Visit 1 can take place while the participant is still in the hospital.

Treatment Period

Following a screening period of up to 2 weeks, eligible participants will be randomized in a 1:1 ratio to either finerenone or placebo. Participants with an eGFR ≤60 mL/min/1.73 m² measured at baseline will start with 10 mg OD (**dose level 1**) with a maximum maintenance dose of 20 mg OD (**dose level 2**), whereas participants with an eGFR >60mL/min/1.73 m² measured at baseline will start with 20 mg OD (dose level 2) with a maximum maintenance dose of 40 mg OD (**dose level 3**).

There will be at least 2 scheduled visits within the first 3 months from randomization, Visit 2 will take place after 1 month and Visit 3 will take place 3 months after randomization; thereafter, scheduled visits will occur every 3 months until Visit 6 at Month 12. After 1 year from randomization, telephone contact visits will take place at Month 14 and from then *onwards* every 4 months (i.e. 18 months, 22 months onwards) *alternating* with on-site visits (i.e. 16 months, 20 months, onwards) until the end of the study is reached.

Up-titration is expected to occur after 4 weeks ± 7 days of treatment at Visit 2 (Month 1). Ideally, each participant will be on the maximum maintenance dose at this point . In the case of elevated potassium values, participants will be down-titrated to the next lower dose. Down-titrations can be performed at any time after the start of study intervention treatment, at any scheduled or unscheduled visit. At any scheduled or unscheduled visit, the dose of study intervention may be increased to the next possible higher dose, based on serum/plasma potassium level and provided the participant was already on a stable dose for 4 weeks ± 7 days.

Participants will attend an additional unscheduled safety visit 4 weeks ± 7 days after each up-titration; potassium levels and renal function will be monitored at this safety visit.
In addition to the protocol-specified visits, participants may be seen at any time throughout the study at the discretion of the investigator.

If, in the opinion of the investigator, the participant cannot tolerate the maximum dose level of study intervention, the study intervention dose may be reduced to the next lower dose level. Provided the participant's safety is not affected, and if considered appropriate by the investigator, the participant should be re-up-titrated to the next higher dose level as soon as possible, preferably within 4 weeks, with the goal of keeping the participant on the maximum tolerated dose level for as long as possible. If the study intervention is temporarily interrupted, it should be re-introduced as soon as medically acceptable in the opinion of the investigator without compromising the participant's safety. See also Sections 6.1 and 7.1.1 for details.

Changes in the study intervention dose, including interruption/premature discontinuation or restart of study intervention, must be recorded in the electronic case report form (eCRF).

It is planned that all randomized participants will remain in the study until either:

a. an instruction is received from the sponsor after the targeted number of primary endpoint events have occurred

or

b. the study is terminated early at the recommendation of the independent DMC.

After randomization, study intervention discontinuation does not constitute the participant's withdrawal from the study, and all participants should continue to be followed up according to the Premature Discontinuation SoA (Figure 1–2).

All randomized participants, including any participant who experiences an event considered for the pre-specified primary or secondary endpoints, should continue to receive double-blinded treatment until the study is completed, provided there are no safety grounds for discontinuing treatment.

Post-treatment Follow-up Period

The period between a participant's last intake of study intervention and last visit in the study is referred to as the '*post-treatment follow-up period*'.

In the event of premature discontinuation of study intervention, participants are expected to continue to attend all protocol-specified study visits, and are expected to perform all scheduled assessments as described in the Premature Discontinuation SoA (Figure 1–2).

Any participant still taking study intervention at the point of end of study will enter the post-treatment follow-up period after stopping study intervention at the EOS Visit.
For these participants, this phase will last 30 +5 days, and will end upon completion of the PT Visit (a telephone call visit; see Figure 1–1).

4.2 Scientific Rationale for Study Design

The inclusion and exclusion criteria allow the selection of an appropriate participant population and increase the likelihood of producing reliable and reproducible results, while guarding against exploitation of vulnerable persons. The proposed criteria are based on existing clinical knowledge and feedback from key opinion leaders involved in treatment of HF (NYHA II-IV).

4.3 Justification for Dose

Finerenone has been investigated with respect to safety, tolerability, pharmacodynamics and pharmacokinetics (PK) in 27 Phase 1 clinical pharmacology studies. PK were also investigated in all five Phase 2 studies for finerenone (CHF and CKD) with a total of 2017 patients.

The dose regimen of finerenone has been selected based on the results of the completed Phase 2b ARTS-HF and ARTS-DN studies.

The proposed doses for this Phase 3 study are as follows:

- For participants with an eGFR ≤60 mL/min/1.73 m^2 at baseline, the starting dose is 10 mg OD. From Visit 2 (Month 1) onwards and if potassium ≤5.0 mmol/l and eGFR decrease is <30%, the starting dose can be up-titrated to 20 mg OD

  and

- For participants with an eGFR >60 mL/min/1.73 m^2 at baseline, the starting dose is 20 mg OD. From Visit 2 (Month 1) onwards and if potassium is ≤5.0 mmol/l and eGFR decrease is <30%, the starting dose can be up-titrated to 40 mg OD.

Note: eGFR according to local laboratory values.

The following rationale for extrapolation to patients with LVEF ≥40% of this dose regimen is based on the expected safety profile of finerenone and the applicability of the exposure/response model founded on ARTS-HF data.

In the RALES study, the effect of spironolactone versus placebo on the outcome of patients with HFrEF was investigated and in the TOPCAT trial, HFpEF patients were treated either with spironolactone or placebo. In both studies, changes of serum potassium under spironolactone seem to occur in a similar time-dependent manner in HFpEF and HFrEF patients (Pfeffer et al. 2015).

In addition, the dose-response relationship is comparable in these two HF populations with potassium increases by 0.37 mmol/L after 3 months of treatment with spironolactone 25 mg in RALES and 0.3 mmol/L after 8 months of treatment with spironolactone in an average dose of 21.7 mg in TOPCAT.

Regarding effects on renal parameters, the dose-response relationship for spironolactone seen in the TOPCAT trial in HFpEF patients and the RALES trial in HFrEF patients was similar indicating that differences in LVEF are not expected to have clinically relevant influence on eGFR changes from baseline (serum creatinine change of 0.16 mg/dL after 8 months for average dose of 21.7 mg in TOPCAT and of 0.10 mg/dL after 3 months for 25 mg spironolactone in RALES).

Overall, the exposure/response relationship for both parameters in HFrEF patients is considered to be applicable for extrapolation to HFpEF patients under the assumption that baseline characteristics with regards to factors influencing PK such as body weight, and

baseline eGFR and baseline potassium levels are similar to that in the ARTS-HF study population. Under these conditions, the expected change of serum potassium is 0.1, 0.2 and 0.2 mmol/L and the expected relative eGFR change from baseline is 2.4, 3.1 and 3.8% for 10, 20 and 40 mg finerenone respectively in the total HF population. These ranges are expected to already represent the worst case scenario since approximately 79% of the ARTS-HF populations are patients with eGFR ≤60 mL/min/1.73 m^2.

Rationale for finerenone 10 mg OD as minimal dose:

10 mg OD will be the minimal dose for the overall population. Up-titration will occur based on potassium and eGFR values and the investigator will have the option to down-titrate this finerenone dose based on its tolerability in terms of potassium values. This 2-step up-titration is consistent with current clinical practice to initiate treatment at a low dose, and to up-titrate the drug only if tolerated in order to avoid adverse effects on potassium and renal parameters.

In ARTS-HF, the 10-20 mg OD finerenone group compared to eplerenone showed a meaningful reduction in the exploratory composite endpoint comprising death from any cause, CV death, time to first CV hospitalizations and emergency presentation for worsening HF. Finerenone 10-20mg OD showed a similar safety profile as to that of eplerenone with a lower incidence of treatment-emergent adverse events and similar rate of hyperkalemia (K^+ ≥5.6 mmol/L) (Filippatos et al. 2016).

In ARTS-DN, significant reductions in UACR at Day 90 compared to baseline were observed for 7.5 mg, 10 mg and 20 mg OD finerenone compared to placebo (Bakris et al. 2015). For the 10 and 20 mg doses, albuminuria had not returned to values similar to those at baseline 30 days after completion of treatment with finerenone suggesting a potential long-lasting effect of finerenone in structural changes in the kidney.

Rationale for finerenone 20 mg OD as maximal maintenance dose in patients with eGFR ≤60 mL/min/1.73 m^2:

A retrospective analysis of a national cohort (Einhorn et al. 2009) comprising 2,103,422 records from 245,808 veterans with at least 1 hospitalization and at least 1 inpatient or outpatient serum potassium record during the fiscal year 2005 showed that CKD and treatment with blockers of RAAS were the key predictors of hyperkalemia. The risk of hyperkalemia is increased with CKD, and its occurrence increases the odds of mortality within 1 day of the event.

Furthermore, patients with an age of 65 years or more with comorbid illness have the highest mortality when potassium levels rises above 5 mmol/L (Pitt et al. 2014a).

It was demonstrated in a subgroup analysis of the finerenone ARTS-HF study that potassium levels >6 mmol/L and eGFR decrease >40% were mainly found in the subgroup with eGFR ≤60 mL/min/1.73m^2 and UACR >300 mg/g (71% of the total population). Based on this data that showed an increase of finerenone concentrations in patients with impaired renal function associated with an increased risk of hyperkalaemia and eGFR reduction, it was decided to limit finerenone maximum dose among patients with eGFR <60 mL/min/1.73m^2.

Rationale for finerenone 40 mg OD as maximal maintenance dose in patients with eGFR > 60 mL/min/1.73 m^2:

NT-proBNP seems to be predictive for clinical outcome for both HFpEF and HFrEF patients. The prognosis of a patient depends on the NT-proBNP level and is similar in both HF populations (Kang et al. 2015). However, the responsiveness of this biomarker to MRAs seems to differ in patients with HFrEF and HFpEF. NT-proBNP was significantly reduced compared to baseline in the eplerenone arm of the EPHESUS study in HFrEF patients (Zannad et al. 2011) and in the ARTS-HF finerenone study (Filippatos et al. 2016). However, the initially observed difference to the placebo arm after 14 months vanished after 26 months in the RAAM-pEF study in HFpEF patients (Deswal et al. 2011). Spironolactone treatment was also found to decrease serum NT-proBNP levels in HFrEF patients (Ozkara et al. 2007), (Pitt et al. 2013). In the TOPCAT trial in HFpEF patients, however, hazard ratios for NT-proBNP terciles were reported to be all >1 indicating that spironolactone did not lead to a significant NT-proBNP change compared to placebo. Furthermore, a meta-analysis assessing MRA treatment in HFpEF patients showed that no reduction of BNP or NT-proBNP was observable in overall 5 studies (Chen et al. 2015). The only trial reporting significant changes in NT-proBNP in HFpEF patients was the ALDO-DHF study with a relatively stable HF population having only few comorbidities due to the study design (Edelmann et al. 2012).

Dose-response relationships for NT-proBNP for either spironolactone or eplerenone in HFpEF and HFrEF patients have not been reported so far, which makes it difficult to assess whether or not it is possible to bridge exposure/response models for NT-proBNP between these populations.

There are uncertainties associated with the responsiveness of NT-proBNP to MRAs. No *quantitative* prediction as to the changes of NT-proBNP for different finerenone doses were performed with an exposure/response model built on ARTS-HF data for finerenone in HFrEF patients. However, from a *qualitative* perspective, a linear exposure response from 2.5mg up to 20 mg has been observed in the ARTS-HF trial indicating that NT-proBNP response was not saturated at 20 mg. This would suggest the possibility of greater effects on NT-proBNP at doses higher than 20 mg.

40 mg OD is the maximum maintenance dose of finerenone in patients with eGFR >60 mL/min/1.73 m^2. When the expected systemic finerenone exposure in these patients with mild renal impairment or normal renal function is compared with observed data in patients with moderate renal impairment receiving finerenone 20 mg in ARTS-HF, largely overlapping exposures are noted due to the effect of moderate renal impairment on area-under the curve (AUC; about 50% increase). These considerations on exposure in patients receiving 40 mg are complemented by exposure/response (PK/pharmacodynamics) analyses and simulations based on data from ARTS-HF. Changes in serum potassium and eGFR from baseline following administration of finerenone 40 mg to patients with normal renal function or mild renal impairment were also estimated to largely overlap with changes following administration of finerenone 20 mg to patients with moderate renal impairment. Generally, the drug effect on serum potassium and eGFR is estimated to be rather small even for 40 mg, compared to the impact of baseline values of the respective parameters. Based on model simulations, the expected change in steady-state serum potassium and eGFR following administration of finerenone 10, 20 and 40 mg OD to the HF population is an increase by 0.1, 0.2 and 0.2 mmol/L and a decrease by 2.4, 3.1 and 3.8%, respectively.

The safety of the 40 mg dose in patients with an eGFR >60 mL/min/1.73 m^2 will also be ensured by the starting dose of 20 mg with escalation to 40 mg only after measuring serum potassium and eGFR levels, and the possibility of down-titration.

Moreover, doses of 40 mg and higher have previously been found to be safe and well tolerated in the Phase 1 program in healthy volunteers, where 80 mg was the highest investigated single dose and 40 mg OD was the highest studied multiple dose regimen. Finerenone PK were linear across the investigated dose range.

In light of the aforementioned aspects, in particular with no reliable surrogate parameter and no additional information beyond the results from ARTS-HF and ARTS-DN to be expected, a specific dose-finding study in patients with HFpEF was not considered necessary.

Details of the results of the clinical and non-clinical development studies conducted with finerenone can be found in the Investigator Brochure.

4.4 End of Study Definition

The end of study treatment period will be announced when the targeted number of primary endpoint events has occurred, unless the study is terminated early because of a recommendation of the DMC.

After notification of study end, an EOS Visit should be scheduled as soon as possible (but within 4 weeks at the latest) for all participants still participating in the study, to determine whether the participant had an event for inclusion in the primary or secondary endpoints.

The date on which the final participant performed the EOS visit is defined as the primary completion date (see schema in Section 1.2).

Participants still on treatment will stop study intervention treatment at the EOS Visit and must perform the PT Visit 30 +5 days after their last dose of study intervention.

Participants no longer taking study intervention must also be contacted as soon as possible after issue of the notification of end of study and be asked to attend the EOS Visit.

For participants who have objected to releasing further information after withdrawing from the study, an updated vital status should be obtained by the investigator from publicly available data sources, wherever allowed by local regulations. The collection of vital status must be obtained within the timelines provided by the sponsor at this time.

The end of the trial as a whole is defined as the date of the last PT Visit of the last participant in the trial globally.

5. Study Population

Patients with a diagnosis of HF, NYHA class II–IV, and documented LVEF of ≥40%.

Prospective approval of protocol deviations to recruitment and enrollment 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 aged 40 years and older, at the time of signing the informed consent.

Type of Participant and Disease Characteristics:

2. Diagnosis of heart failure with NYHA class II–IV, ambulatory or hospitalized primarily for heart failure (if a hospitalized patient cannot be randomized as an in-patient, randomization as soon as possible after discharge is encouraged)

3. Treated with diuretics within 30 days prior to randomization

4. Documented LVEF of ≥40% measured by any modality within the last 12 months, at the latest at screening; if several values are available, the most recent one shall be reported. If LVEF was not measured in the past 12 months, a new measurement may be done at screening

5. Structural heart abnormalities based on any local imaging measurement within the last 12 months, latest at screening, defined by at least 1 of the following findings:
   - LAD ≥3.8cm, LAA ≥20cm^2, LAVI >30 mL/m^2, LVMI ≥115 g/m^2 (♂) / 95 g/m^2 (♀), septal thickness or posterior wall thickness ≥1.1 cm

6. NT-proBNP ≥300 pg/mL (BNP ≥100 pg/mL) in sinus rhythm or NT-proBNP ≥900pg/mL (BNP ≥300 pg/mL) in atrial fibrillation (or if atrial fibrillation status is unknown; see Section 4.1) for participants [1] obtained at the following time:
   - **Within 90 days prior to randomization** if patient had been **hospitalized for HF** requiring initiation or change in HF therapy or if patient had an **urgent visit for HF** requiring intravenous (IV) diuretic therapy, both within 90 days prior to randomization

   OR

   - **Within 30 days prior to randomization** if patient has **not** been hospitalized for HF nor had an urgent HF visit within the past 90 days.

[1] If a participant is being treated with Entresto (sacubitril/valsartan), the NT-proBNP value only (not BNP) should be used.

Sex

7. Male or female.

   Women of childbearing potential can only be included in the study if a pregnancy test is negative at screening and baseline and if they agree to use adequate contraception which is consistent with local regulations regarding the methods for contraception for those participating in clinical trials.

Informed Consent

8. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 Exclusion Criteria

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

Medical Conditions

1. eGFR <25 mL/min/1.73 m² at either screening or randomization visit.
   NOTE: one reassessment of eGFR is allowed at the screening and randomization visit, respectively
2. Serum/plasma potassium >5.0 mmol/L at either screening or randomization visit.
   NOTE: one reassessment of potassium is allowed at the screening and randomization visit, respectively
3. Acute inflammatory heart disease, e.g. acute myocarditis, within 90 days prior to randomization
4. Myocardial infarction or any event which could have reduced the ejection fraction within 90 days prior to randomization
5. Coronary artery bypass graft surgery in the 90 days prior to randomization
6. Percutaneous coronary intervention in the 30 days prior to randomization
7. Stroke or transient ischemic cerebral attack within 90 days prior to randomization
8. Probable alternative cause of participants' HF symptoms that in the opinion of the investigator primarily accounts for patient's dyspnea such as significant pulmonary disease, anemia or obesity. Specifically, patients with the below are excluded:
   - Severe pulmonary disease requiring home oxygen, or chronic oral steroid therapy
   - History of primary pulmonary arterial hypertension
   - Hemoglobin <10 g/dl
   - Valvular heart disease considered by the investigator to be clinically significant
   - Body mass index (BMI) >50 kg/m^2 at screening
9. Systolic blood pressure (SBP) ≥160 mmHg if not on treatment with ≥3 blood pressure lowering medications or ≥180 mmHg irrespective of treatments, on 2 consecutive measurements at least 2-minute apart, at screening or at randomization

10. Life-threatening or uncontrolled arrhythmias at screening and/or randomization including but not limited to sustained ventricular tachycardia and atrial fibrillation, or atrial flutter with resting ventricular rate >110 bpm
11. Symptomatic hypotension with mean systolic blood pressure <90 mmHg at screening or at randomization
12. Any primary cause of HF scheduled for surgery, e.g. valve disease such as severe aortic stenosis or severe mitral regurgitation by the time of screening or randomization
13. History of peripartum cardiomyopathy, chemotherapy induced cardiomyopathy, viral myocarditis, right heart failure in absence of left-sided structural disease, pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy including amyloidosis
14. Presence of left ventricular assist device by the time of screening or randomization
15. History of hyperkalemia or acute renal failure during MRA treatment for >7 consecutive days, leading to permanent discontinuation of the MRA treatment
16. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotrophin urine or serum test
17. Known hypersensitivity to the study intervention (active substance or excipients)
18. Hepatic insufficiency classified as Child-Pugh C at screening or randomization
19. Addison's disease.

Prior/Concomitant Therapy

20. Requirement of any IV vasodilating drug (e.g. nitrates, nitroprusside), any IV natriuretic peptide (e.g. nesiritide, carperitide), any IV positive inotropic agents, or mechanical support (intra-aortic balloon pump, endotracheal intubation, mechanical ventilation, or any ventricular assist device) within 24 hours prior to randomization
21. Participants who require treatment with **more than one** ACEI, ARB or angiotensin-receptor neprilysin inhibitor (ARNI), or **two simultaneously at randomization**
22. Continuous (at least 90 days) treatment with an MRA (e.g. spironolactone, eplerenone, canrenone, esaxerenone) within 12 months prior to screening. Last intake at least 30 days before randomization. Treatment with MRA should not be interrupted with the purpose of enrollment into the study
23. Concomitant treatment with any renin inhibitor or potassium-sparing diuretic that cannot be stopped prior to randomization and for the duration of the treatment period
24. Concomitant systemic therapy with potent cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors or inducers that cannot be discontinued 7 days prior to randomization and for the duration of the treatment period (e.g. itraconazole, ritonavir, indinavir, cobicistat, clarithromycin).

Other Exclusions

25. Any other condition or therapy, which would make the participant unsuitable for this study and will not allow participation for the full planned study period (e.g. active malignancy or other condition limiting life expectancy to less than 12 months)
26. Previous assignment to treatment during this study
27. Participation in another interventional clinical study (e.g. Phase 1 to 3 clinical studies) or treatment with another investigational medicinal product within 30 days prior to randomization
28. Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site)
29. Known current alcohol and/or illicit drug abuse that may interfere with the participant's safety and/or compliance at the discretion of the investigator
30. Participant is in custody by order of an authority or a court of law.

5.3 Lifestyle Considerations

No restrictions during the study are required other than those specified in 'Other Exclusions'.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly 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 (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (including reason), and eligibility criteria.

If a participant is not eligible at the Screening Visit for this study (20103), the participant may be re-screened once at a later time, provided the investigator believes that a change in the participant's condition makes him/her potentially eligible.

The following conditions are pre-requisites of re-screening:

1. Before re-screening, new written informed consent must be obtained
2. Allocation of a new participant number
3. All assessments for the study must be repeated
4. At least 3 months between initial screening and rescreening.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

The IxRS will determine the medication numbers for the study site investigator or designee to select for the participant.

Eligible participants will receive study intervention at the doses illustrated in Table 6–1, dispensed as outlined in the SoA (Section 1.3). The dose of finerenone will depend on the eGFR value at the Baseline Visit (determined by the local laboratory):

1. Participants with an eGFR ≤60 mL/min/1.73m² will start with 10 mg (dose level 1) and have a maintenance dose of 20 mg (dose level 2). Dose level 1 is the minimum dose and dose level 2 is the maximum permitted dose in this group of patients
2. Participants with an eGFR >60 mL/min/1.73m² will start with 20 mg (dose level 2) and have a maintenance dose of 40 mg (dose level 3). Dose level 1 is the minimum dose and dose level 3 is the maximum permitted dose in this group of patients.

The investigator is encouraged to up-titrate the dose of study intervention once the participant has been on a stable dose for 4 weeks (±7 days), either at the next regular visit or at an Up-titration Visit (see Table 6–1). Participants who do not tolerate their starting dose of 20 mg may be down-titrated at any point during the study, including between-scheduled visits if required for safety reasons. These participants may be up-titrated again based on the rules provided in Table 6–1. If the participant is already at the minimum dose, the study intervention can be interrupted at the investigator's discretion as detailed in Section 6.6, based on blood potassium levels and renal function which will be monitored throughout the study.

Intake of study intervention

Participants will be instructed to take one tablet of study intervention, preferably in the morning, at approximately the same time each day. The study intervention should be taken with a glass of water, with or without food.

Note: On the day of the first PK visit (Month 3) the participant should be instructed not to take the tablet at home in the morning but to have the PK sample collected first and then to take the study intervention at the study site.

Table 6–1 Dosage of study intervention for administration

eGFR value at the Baseline Visit, based on local laboratory results:	**eGFR 25 to ≤60 mL/min/1.73m²**		**eGFR >60 mL/min/1.73m²**	
Participant randomized to group:	**Finerenone**	**Placebo**	**Finerenone**	**Placebo**
Starting dose:	10 mg finerenone OD (**Dose Level 1**)	Placebo OD	20 mg finerenone OD (**Dose Level 2**)	Placebo OD
Maintenance dose:	20 mg finerenone OD (**Dose Level 2**)	Placebo OD	40 mg finerenone OD (**Dose Level 3**)	Placebo OD
Minimum dose after down-titration:	10 mg finerenone OD	Placebo OD	10 mg finerenone OD	Placebo OD
Maximum dose after up-titration:	20 mg finerenone OD	Placebo OD	40 mg finerenone OD	Placebo OD
Study intervention intake	One tablet of study intervention OD, preferably in the morning at approximately the same time each day. Note: Study intervention will be administered at home, except on the day of the first PK visit when the tablet will be taken at the study site			
Missed intake	• If discovered within 16 hours after the scheduled time, the participant should take one tablet of study intervention as soon as possible • If discovered >16 hours after the scheduled time, this will be considered to be a 'missed' dose and the participant should wait and take the next tablet of study intervention at the usual (scheduled) time.			
Up-titration of dose • From Visit 2 (Month 1) onwards, at any scheduled or unscheduled visit • Follow guidance in Table 6–2 and Table 6–3 • Perform an additional safety visit 4 weeks ±7 days after each titration; monitor* potassium and renal function • Must be documented in the eCRF	Finerenone • Up-titrate study intervention to the next possible higher dose based on serum/plasma potassium level • eGFR decrease is <30% compared to last scheduled visit. Placebo • Sham-titrate.			
Down-titration of dose • At any scheduled or unscheduled visit • Follow guidance in Table 6–2 and Table 6–3 • Perform an unscheduled safety visit within an adequate timeframe proposed by the investigator; monitor* potassium and renal function • Must be documented in the eCRF	• If potassium ≥5.5, down-titrate to the next lower dose level in a step-wise manner (dose level 2 to 1, or dose level 3 to 2) • If at dose level 1, interrupt study intervention treatment; study intervention should be re-introduced at dose level 1 as soon as the investigator considers it to be medically justified without compromising safety • If in the opinion of the investigator, the participant cannot tolerate the maximum dose level of study intervention, the study intervention dose may be reduced to the next lower dose level.			

Abbreviations: eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; OD = once daily, PK = pharmacokinetics

***** NOTE: Potassium and eGFR according to local laboratory values

6.2 Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit if applicable, for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be kept in a secure environment and stored as per the instructions on the label.
3. The investigator or the head of the institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Investigator Site File.

6.3 Measures to Minimize Bias: Randomization and Blinding

Eligible participants will be centrally assigned to randomized study intervention at Visit 1 using an IxRS. The randomization will be stratified by country/region and LVEF (<60%, ≥60%). Additional details will be described in the SAP.

Treatment allocation will be done according to a computer-generated randomization list specified by the sponsor's responsible statistician and provided by the sponsor's randomization management group. Additional details are documented in the IxRS instruction manuals.

Study intervention will be dispensed at the study visits summarized in the SoA. Returned study intervention should not be re-dispensed to the participants.

Tablets containing 10 mg and 20 mg finerenone immediate-release (IR) tablets will differ in size from 40 mg finerenone IR tablets, but will be identical in appearance (size, shape, color) to matching placebo tablets. The packaging and labeling will be designed to maintain the blinding of the investigator's team and the participants. The study data will remain blinded until database lock and authorization of data release according to standard operating procedures.

In compliance with applicable regulations, in the event of a suspected unexpected serious adverse reaction (SUSAR) related to the blinded treatment, the participant's treatment code will usually be unblinded before reporting to the health authorities and ethics committees. For further details, see Section 8.3.6. Bioanalytical staff will be unblinded according to the corresponding Bayer standard operating procedure (SOP). Pharmacometrics staff may also be unblinded according to Bayer SOPs. Appropriate measures will be taken to maintain blinding of the study team, e.g. data will be stored separately, and members of the study team will neither have access to the randomization list nor to individual data.

The IxRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the responsibility for determining if unblinding of a participant's treatment assignment is warranted. If the investigator is unavailable, and a treating physician not associated with the study requests emergency unblinding, the emergency unblinding requests are forwarded to the study specific emergency medical advice 24 hours/7 day service. The participant's safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours

after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

6.4 Study Intervention Compliance

To monitor compliance, the investigator will be required to complete a drug dispensing log for each participant. The date of dispensing the study intervention to the participant will be documented.

Overall compliance with study intervention intake should be between 80% and 120% of the scheduled dose at the end of study intervention treatment.

Study intervention will be dispensed according to the schedule provided in the SoA (Section 1.3). Participants will be instructed to bring all unused study intervention and empty packages at every (un)scheduled visit for accountability purposes. Any discrepancies between actual and expected amount of returned study medication must be discussed with the participant at the time of the visit, and any explanation must be documented in the source documents.

6.5 Prior and Concomitant Therapy

General considerations

To date, there has been no treatment showing mortality or morbidity benefit in participants with HFpEF and thus, pharmacologic treatments for HFpEF typically manage symptoms with diuretics being recommended in congested participants in order to alleviate symptoms and signs of HF.

Arterial hypertension is highly prevalent among patients with HFpEF preceding the development of HF and contributing to CV morbidity and mortality by causing substantial CV structural and functional abnormalities by activating the RAAS.

To ensure that a relevant contributor to the development of HF and its outcome is well controlled, participants with uncontrolled blood pressure will be excluded; the treatment of comorbidities in particular arterial hypertension will be at the discretion of the investigator.

All concomitant medication until a participant's last visit will be recorded in the eCRF.

Concomitant therapies **not permitted during treatment with study intervention** are:

- Eplerenone, spironolactone, canrenone, esaxerenone, any renin inhibitor, or potassium-sparing diuretic
- **More than one** of the following: ACEI, ARB, ARNI
- Potent CYP3A4 inhibitors or inducers.

Drug interactions to look out for

The following should be used with caution, at the discretion of the investigator on a case-by-case basis:

- Potassium supplementation
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Trimethoprim and trimethoprim / sulfamethoxazole

- Any other medication known to raise potassium levels and/or cause deterioration in renal function.

The investigator is expected to regularly assess the participant's potassium levels and/or renal parameters (e.g. eGFR, creatinine), especially for those receiving these medications. For further details, see the SoA (Section 1.3).

Potassium-lowering agents (e.g. sodium polystyrene sulfonate, calcium polystyrene sulfonate) are allowed to be started during treatment with study intervention following their labeled indication.

Any use of potassium supplementation and potassium-lowering agents must be documented in the eCRF.

A list of the most common CYP3A4 inhibitors and inducers will be provided.

Caution

Increases in finerenone exposure in combination with the following weak or moderate CYP3A4 inhibitors cannot be excluded: amiodarone, aprepitant, bicalutamide, chloramphenicol, dasatinib, imatinib, lapatinib, mifepristone, nilotinib, norfloxacine, tacrolimus, verapamil. Caution should also be exercised with concomitant use of high-dose acetylsalicylic acid (>500 mg/day).

In vitro data suggest a weak interaction for the highest dose of finerenone (40mg) with BCRP (Breast Cancer Resistance Protein) and OATP (Organic Anion Transporter Polypeptide) transporters. A clinically relevant drug-to-drug interaction at a dose of 40mg finerenone is considered unlikely, but cannot be excluded. BCRP/OATP substrates include some statins (e.g. atorvastatin, simvastatin, rosuvastatin, fluvastatin, pitavastatin, pravastatin) and other substances (e.g. methotrexate, sulfasalazine, glibenclamide, repaglinide). A list of BCRP/OATP substrates will be provided.

If finerenone is given concomitantly with other drugs that may increase the exposure of BCRP/OATP substrates, the respective drug labels should be consulted.

6.5.1 Rescue Medicine

Not applicable.

6.6 Dose Modification

As described in Sections 6.6.1 and 4.3, the dose of study intervention should be adjusted (up-or down-titration) on the basis of potassium and eGFR levels.

6.6.1 Monitoring of Blood Potassium and Dose Adjustment

Guidance for the adjustment of dose after start of study intervention intake based on serum/plasma potassium levels is provided in Table 6–2.

Table 6–2 Potassium levels and guidance for dose adjustment

Serum / plasma potassium (K^+ mmol/L)		Action to be taken
First sample:		
<5.0		Increase to the next higher dose level (or continue at maximum permitted dose level)
≥5.0 to <5.5		Continue the current dose level
≥5.5 to <6.0		Down-titrate to the next lower dose if possible, if patient already on dose level 1 interrupt study intervention and check K^+ within 72 h; follow **option a**
≥6.0		Interrupt study intervention and check K^+ within 72 h; follow **option b**
Second and subsequent sample:		
Option a	**<5.5**	Continue current dose
	≥5.5	Down-titrate to the next lower dose if possible, or interrupt study intervention and recheck K+
Option b	**<5.5**	Restart at dose level 1
	≥5.5	Continue to withhold study intervention, further monitoring of K^+. Restart at dose level 1 **ONLY** if K^+ is <5.0 mmol/L

The following aspects have also to be taken into consideration:

1. If the participant is already on dose level 1 no further decrease is possible after interruption, the same dose level should be re-started once serum/plasma potassium falls below 5.5 mmol/L. Serum/plasma potassium is to be measured at a safety visit 4 weeks ± 7 days after re-starting treatment or dose adjustment.
2. If the participant is on dose level 1 of study intervention, but hyperkalemia recurs soon after a previous event of hyperkalemia leading to interruption of study intervention, and there is no explanation for the recurring hyperkalemia event other than intake of study intervention, premature and permanent discontinuation of study intervention is recommended.
3. In case of hyperkalemia, it is at the investigator's discretion to take measures, including treatment and monitoring in accordance with local practice standards, beyond those reflected in Table 6–2.

6.6.2 Monitoring of Renal Function and Dose Adjustment

The dose of study intervention can be adjusted at the discretion of the investigator to account for renal function following the recommendations displayed in the table below Table 6–3.

Table 6–3 Renal function evaluation during study

eGFR (mmol/L/1.73 m²) at any time after randomization	**Action to be taken**
Decrease ≥25% and <40% from baseline	1. Check for potential reversible causes: a. Concomitant medications known to affect renal function (e.g. NSAIDs, antibiotics) b. Adverse event (e.g. urinary infection, urinary retention, dehydration) 2. Address potential reversible causes if considered clinically appropriate
Decrease ≥40% from baseline	1. Check for potential reversible causes and address, as above. 2. At the investigator's discretion, study drug can be down-titrated or interrupted as follows: • Re-test after 4 weeks to confirm eGFR decrease> 40% as secondary endpoint * • Further monitor eGFR/creatinine • If eGFR/creatinine has reached acceptable levels (to be determined for the individual participant), please re-start study intervention at the next lower dose level (or dose level 1 if the participant was already on this dose).

Abbreviations: eGFR = estimated glomerular filtration rate; NSAID = non-steroidal anti-inflammatory drug
* Decrease of > 40% based on central laboratory data.

6.7 Intervention After the End of the Study

No intervention is planned following the end of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

After randomization, discontinuation of study intervention (for any reason) does not constitute the participants' withdrawal from the study (see also Section 7.2).

Study intervention must be prematurely and permanently discontinued if any of the following occurs:

- Pregnancy of the participant (see also Section 8.3.5)
- The investigator is of the opinion that continuation of treatment with study intervention is harmful to the participant's well-being
- The randomization code is broken by the investigator, or other responsible person, when knowledge of the participant's treatment is required
- Any investigational drug other than the study intervention is used.

Study intervention *may* be prematurely and permanently discontinued if any of the following occurs:

- Any suspected drug-related AE or SAE
- If any exclusion criterion applies during treatment
- Participant requires treatment with an MRA (eplerenone, spironolactone, exerenonone)
- If a significant violation of the protocol occurs, as defined by the sponsor and the coordinating investigator.

Participants who prematurely and permanently discontinue study intervention are expected to continue in the post-treatment follow-up period and to attend all protocol-specified study visits, and should be encouraged to perform all scheduled assessments described in the SoA for premature discontinuations (Figure 1–2).

If a participant no longer on study intervention is unable to attend the clinic for a study visit, a telephone consultation may be performed to determine if relevant health events /endpoints (e.g. development of CV or renal complications) have occurred. Ideally, a face-to-face visit should be performed at least once a year. Expected frequency of telephone contacts should be in line with the standard visit schedule, and therefore performed every 4 months. Ad hoc additional telephone contacts may also be requested (e.g. prior to the interim analysis) and made to the participant themselves or to other contact as provided by the patient, e.g. next of kin, primary physician (or local equivalent).

Note that study intervention may be temporarily discontinued (i.e. interrupted), as described in Section 6.6.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary Discontinuation

Resumption of study intervention after temporary interruption

Upon temporary interruption of the study intervention due to hyperkalemia, eGFR decrease, (S)AE, outcome events (OE), intolerability or any other reason, intake should be resumed as soon as medically acceptable at the discretion of the investigator. There is no defined maximum time limit for temporary interruption. In all cases, the reason for study intervention interruption must be recorded in the eCRF and the participant's medical records.

If the study intervention is interrupted for more than 7 days, the re-start should be performed at the next lower dose and the investigator should schedule an up-titration visit after 4 weeks (± 7 days) in order to monitor potassium levels and renal function (see Table 6–1). If a regular visit will be scheduled to take place 4 weeks ± 7 days after up-titration or re-start, the monitoring of potassium and renal function is assured and no up-titration visit has to be performed in addition.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, a premature discontinuation visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of study discontinuation and check for any further evaluations that need to be completed.
- The participant may be prematurely and permanently discontinued from the study intervention at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

General Procedure for Discontinuation/Withdrawal

In all cases, the reason for withdrawal of study intervention and/or of study participation must be recorded in the eCRF and in the participant's medical records.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she 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 clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, every effort should be made to contact him/her or a knowledgeable informant (e.g. family doctor, close relative, as indicated in the participant's medical records) by telephone to ask if any of the primary, secondary, or other endpoints have been reached at the scheduled visits for the remaining duration of the study. Attempts to contact the participant should be documented in the participant's records. If any participant refuses to be contacted by telephone (e.g. withdrawal of consent), every effort should be made to obtain vital status (alive or dead) information through consultation of public databases, wherever allowed by local regulation.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor 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, 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 subject enrollment/identification log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g. blood tests) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- All procedures and assessments should be conducted on the day of the visit (see Section 1.3).

8.1 Efficacy Assessments

All efficacy evaluations will be conducted according to the schedule detailed in the SoA.

The KCCQ and EQ-5D-5L are available in a high number of validated translations. Participants should complete each questionnaire alone and prior to the commencement of the other study visit procedures. However, participants in whose language a validated translation of the KCCQ or EQ-5D-5L is not available will be exempt from completing the questionnaire.

Participants who require visual aids (e.g. eye glasses) to read but forgot to bring them may be exempted from completing the questionnaire for that visit. The reason(s) for non-completion of the questionnaires are to be recorded.

8.1.1 Kansas City Cardiomyopathy Questionnaire (KCCQ) and Total Symptom Score (TSS)

The **KCCQ** is a patient-reported disease-specific health status measure intended for the assessment of HF patients' perspectives of how their disease impacts their lives (Green et al. 2000). Patients are asked to recall how their HF impacted their life over a 2-week recall period. Response options for the 23 items (questions) are on a 5- to 7-point Likert-type scale with varying response options depending on the question. It requires, on average, 4 to 6 minutes to complete.

The **TSS** domain of the KCCQ was selected as the secondary endpoint because it is a direct measure of the hypothesized improvement of clinical symptoms. HF symptoms are subjective in nature and are best reported by the patient. The frequency and burden of clinical symptoms of HF in daily life include fatigue (KCCQ items 5 and 6), shortness of

breath (KCCQ items 7 and 8), paroxysmal nocturnal dyspnea orthopnea (KCCQ item 9) and patient peripheral edema/swelling (KCCQ items 3 and 4) and are summarized in the TSS.

In addition to the KCCQ TSS, the KCCQ also measures the impact of patients' HF or their treatment in distinct domains: symptoms (with subscores for frequency and burden), physical limitations, quality of life, social limitations, self-efficacy and symptom stability. All scores are transformed to a 0-100 scale, with higher scores indicating a better outcome. The domains of self-efficacy (a measure of patient knowledge of preventing HF exacerbations) and symptom stability (a measure of symptom change over the previous 2 weeks) will not be considered measures of treatment efficacy.

8.1.2 EuroQoL (EQ-5D-5L)

The EuroQol (EQ-5D-5L) is an instrument used to assess the current health status of patients. It consists of 5 domains and one visual analogue scale. This instrument assesses self-reported health-related quality of life across the domains of mobility, self-care, usual activity, pain/discomfort and anxiety/depression of participants with an overall assessment of health status with a visual analog scale.

8.1.3 Patient Global Impression of Change (PGIC) and Severity (PGIS)

The PGIC question asks the patient to assess the degree of change in their HF symptoms compared to the start of the treatment using the following response options: *much better, better, a little better, the same, a little worse, worse* or *much worse*.

The PGIS question asks the patient to assess the current severity of their HF symptoms due to HF using the following response options: *no symptoms, mild, moderate, severe* or *very severe.*

The 2 PGI questions will be administered in a sub-population of approximately 1200 patients, recruited at selected sites, at baseline (PGIS only) and at Visit 4 (Month 6), Visit 5 (Month 9) and Visit 6 (Month 12). They will be used as an anchor to provide an estimate of clinically meaningful in the KCCQ TSS. Details of the analysis, to be described in a separate SAP, will be conducted on a blinded dataset and reported separately from the CSR.

8.1.4 Assessment of NYHA class

NYHA class will be assessed according to the classification below:

- Class I: No limitation of physical activity
- Class II: Slight limitation of physical activity in which ordinary physical activity leads to fatigue, palpitation, dyspnea, or pain from angina; the person is comfortable at rest
- Class III: Marked limitation of physical activity in which less-than-ordinary activity results in fatigue, palpitation, dyspnea, or anginal pain; the person is comfortable at rest
- Class IV: Inability to carry on any physical activity without discomfort but also symptoms of heart failure or the anginal syndrome even at rest, with increased discomfort if any physical activity is undertaken.

8.1.5 NT-proBNP and hs-TnT

NT-proBNP and hs-TnT measurements during the study (including baseline) will be assessed by the central laboratory. NT-proBNP or BNP measurements for eligibility check will be retrieved from medical records or assessed locally at screening.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

Safety assessments will include AEs, physical examination findings (if performed), and vital signs including heart rate and blood pressure assessment. Safety laboratory tests will include blood chemistry, hematology and urinalysis.

8.2.1 BMI and Weight

Body weight (in indoor clothing without shoes) will be measured at screening and all on-site scheduled visits, as weight gain can be the first clinical sign for HF. Height in centimeters will be assessed at screening visit for calculation of BMI. Hip and waist circumference in centimeters will be measured at the screening visit only.

8.2.2 Vital Signs

Vital signs will be assessed at all on-site scheduled visits.

Blood pressure and pulse measurements will be assessed preferably with a completely automated device and should be preceded by at least 10 minutes of rest for the participant in a quiet setting without distractions (e.g. television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 2 pulse and 2 consecutive blood pressure measurements, at least 2 minutes apart in sitting position. All blood pressure measurements will be recorded on the eCRF.

8.2.3 Clinical Safety Laboratory Assessments

Section 10.2 lists the clinical laboratory tests to be performed and the SoA specifies the timing.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g. related to SAE or AE or dose modification), then the results must be recorded in the eCRF.

Central Laboratory Assessment

The name and the address for the central laboratory service provider can be found in the documentation supplied by the vendor. Only centrally analyzed blood samples will be considered for statistical analysis, unless otherwise specified. Details of the collections, shipment of samples and reporting of results by the central laboratory will be provided to the investigators in the Laboratory Manual.

- Laboratory evaluations (hematology, HbA_{1c}, clinical chemistry, urinalysis parameters and biomarkers) are shown in Section 10.2.
- SoA (Section 1.3) for the timing and frequency.

Local Laboratory Assessment

Blood safety samples will be taken from the Screening Visit onwards for analysis at the local laboratory.

- The following clinical chemistry parameters must be measured and the values documented in the eCRF
    - Serum/plasma creatinine (eGFR will be calculated automatically in the eCRF using the CKD-EPI formula)
    - Serum/plasma potassium.

Potassium values should be recorded using a single decimal point (e.g. 4.5 mmol/L or mEq/L). In the event of hyperkalemia, please see Table 6–2 for guidance.

Up-titration or down-titration of the study intervention will be based on local potassium results and must be documented in the eCRF. Down-titration of the study intervention will occur for safety reasons only.

Additionally, at screening, BNP or NT-proBNP can be measured if not available from clinical medical records.

In women of childbearing potential, a pregnancy test will be performed locally, at screening and baseline. Further pregnancy tests should be performed in participants of childbearing potential as required by national/institutional regulations (e.g. at every visit). At any time during study participation, additional pregnancy testing should be performed upon suspicion of pregnancy. Both serological and urine tests are acceptable.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3.

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or health care professional not involved in the study).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. They remain responsible for following up SAEs, or AEs considered related to the study intervention or study procedures, or those that caused the participant to discontinue the study intervention or the study (see Section 7).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs/SAEs will be collected from the start randomization at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of randomization but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section, except those related to study procedure; the latter have to be recorded as (S)AEs after informed consent has been obtained.

A surgical procedure that was planned prior to randomization by any physician treating the participant should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

Disease-related events and/or disease-related outcome events that are specified in the Section 8.3.6 will not be subject to (S)AE documentation. Thus they will not be recorded as SAEs on the AE page and will not be sent to the sponsor. Instead, these events will be recorded on the Outcome Event pages of the eCRF. Consequently, they will neither be unblinded, not reported to regulatory authorities, IECs, or investigators even though the event may meet the definition of an SAE, see Section 8.3.6. All other SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstances should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated safety-relevant SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor 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.

The sponsor 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. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female and, if indicated, female partners of male participants will be collected after the start of study intervention and until the end of the follow-up period.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.

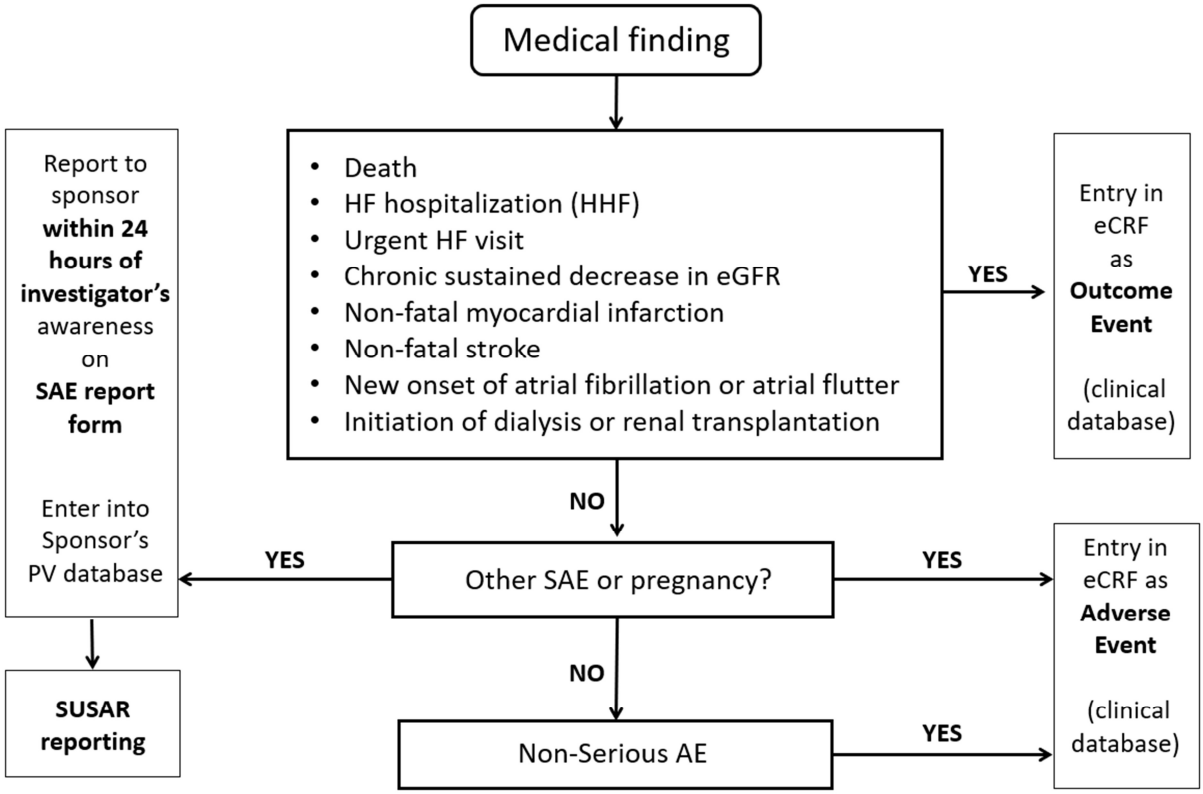
Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The disease related events and/or disease related outcomes events specified in Figure 8-1 will not be documented as (S)AEs. Instead, these events will be documented only on the Outcome Event pages of the eCRF. In addition, they will not be reported as SAEs and will neither be unblinded, nor reported to regulatory authorities, IECs, or investigators (see also Section 8.3.4 for details).

However, they will be collected in the eCRF, monitored by the independent, unblinded DMC during the study and analyzed in the clinical report after end of study. Should unexpected safety issues be identified, specific amendments will be implemented.

Figure 8-1 Medical finding: event versus outcome



Abbreviations: eCRF = electronic case report form, HF = heart failure; (S)AE = (serious) adverse event; SUSAR = serious unexpected suspected adverse reaction

8.4 Treatment of Overdose

Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

In this trial, an overdose is defined as any occasion when the participant has taken (accidentally or intentionally) any dose higher than the maximal target dose prescribed in the protocol.

Overdose following administration of study interventions should be treated as clinically indicated based on symptoms and signs. There is no specific reversal agent for finerenone and the Sponsor does not recommend specific treatment for an overdose.

Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent (see Section 10.3.1).

8.5 Pharmacokinetics

For the investigation of systemic exposure to finerenone and its relationship with treatment effects, the plasma concentrations of finerenone will be determined at different time points using a sparse sampling approach in all participating participants. The plasma concentration versus time data collected on the visits as outlined in SoA (see Section 1.3) will be evaluated descriptively, separated by dose. Plots will be prepared of all individual plasma concentrations vs. actual relative study times (time of sample collection after time of study intervention administration).

The PK data will also be evaluated using non-linear mixed effect modeling (NONMEM). In addition, attempts will be made to identify whether the PK of finerenone is influenced by covariates and to explore exposure-response relationships. This evaluation will be described in a separate analysis plan and will be reported separately.

At Visit 3 (Month 3), a trough sample for the determination of finerenone plasma concentrations will be drawn before intake of study intervention. At this visit, study intervention will be administered at the study site by study personnel and the exact time of study intervention intake on the day before the visit and on the day of the visit and the exact sampling time will be recorded in the eCRF. Ideally, the study personnel should contact the participant prior to Visit 3 to remind them not to take the study intervention as usual in the morning at home.

At Visit 6 (Month 12) and following visits as outlined in SoA (see Section 1.3), one blood sample for the determination of finerenone plasma concentrations will be drawn at any time during the visit after study intervention intake at home. The participants should be advised to take their drug as usual in the morning at home and recall the time of drug intake or note the time of drug intake on the contact card. The exact time of study intervention intake and the exact sampling times will be recorded in the eCRF.

The PK bioanalysis will be performed under the responsibility of Bayer Pharmaceuticals Bioanalytics Laboratory, Bayer AG, BAG-PH-RD-TS-DMPK Bioanalytics, 42096 Wuppertal, Germany.

Details about the collection, processing, storage and shipment of samples will be provided separately (e.g. sample handling sheets or laboratory manual).

8.6 Pharmacodynamics

Analysis of the pharmacodynamics parameters (e.g. blood pressure, heart rate, laboratory values) will be described in detail in the SAP.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

The biomarkers NT-proBNP and hs-TnT will be determined in plasma at the time points indicated in SoA for central laboratory assessments (Section 1.3).

Sample handling and storage - details on the collection, processing, shipment and storage of samples will be provided in separate documents (e.g. sample handling sheets or lab manual). Samples may be stored for a maximum of 15 years (or according to local regulations) following the end of the study at a facility selected by the sponsor to enable further analyses.

Other biomarkers

In addition to the biomarkers described above, other exploratory biomarkers related to e.g. the mode of action or the safety of the study intervention and similar drugs may be investigated. The same applies to further biomarkers deemed relevant to CV diseases and associated health problems. These investigations may include e.g. diagnostic, safety, pharmacodynamic,

monitoring, or potentially predictive biomarkers. Samples (one serum and one plasma) for these analyses will be collected according to the SoA.

The results of biomarker investigations may be reported separately (e.g. in a biomarker evaluation report).

8.9 Immunogenicity Assessments

Not applicable.

8.10 Medical Resource Utilization and Health Economics

Additional analysis will be undertaken to assess the impact of treatment on Healthcare resource utilization, this may include hospitalization (by cause, frequency and duration), urgent heart failure outpatient visits, other treatments, tests and procedures as appropriate.

9. Statistical Considerations

9.1 Statistical Hypotheses

The primary endpoint is the composite of CV death and total (first and recurrent) HF events (HHFs and urgent HF visits). The primary analysis of this endpoint will be performed in the full analysis set using the planned treatment group, in line with the intention-to-treat principle.

Participants without an event of the primary composite endpoint at the time of analysis will be censored at the date of their last contact or date of non-CV death.

The primary analysis of the primary endpoint of the composite will be based on a stratified Andersen-Gill model (Andersen 1982) including treatment group as fixed effect and including country/region and LVEF (<60%, ≥60%) as stratification factors. Robust standard errors (sandwich estimator) will be used to account for correlations of event times within a participant. As shown by (Lin et al. 2000), the Andersen-Gill model with robust standard errors can be interpreted as a proportional rates model. After the authors of that paper, the model is also referred to as the 'LWYY model'. Let θ be the ratio of rates in the finerenone versus placebo group. In order to evaluate whether finerenone is superior to placebo in reducing the rate of the composite event of CV death and total HF events the following null hypothesis will be tested using the model above at a two-sided significance level of 5.0%:

$$H_0: \theta = 1 \quad \text{versus} \quad H_1: \theta \neq 1,$$

where a $\theta < 1$ represents a treatment benefit of finerenone over placebo.

A point estimate of the rate ratio together with a 95% confidence interval will be presented, as well as a plot of the mean cumulative function by treatment group.

In terms of the addendum to ICH E 9 (ICH_E9 (R1) 2019), there are 3 important intercurrent events to consider: Treatment discontinuation, CV death and non-CV death. For treatment discontinuation a treatment policy strategy will be applied, i.e. patients will be followed up for events after discontinuing treatment and these events and the follow-up time will be included in the analysis. CV death will be counted as both an outcome event as well as a censoring event, so that a combination of a composite and a while alive strategy is used. It is thus assumed that patients could have had further events for HF, if they had not died. This

seems appropriate, as including into the model that no further HF events can occur after death, for example by censoring patients at the end of the study, would induce a bias in favor of a treatment group with more early deaths. Non-CV death is assumed to be a censoring event, since the treatment is not assumed to have an effect on these events and interest lies in the treatment effect on composite events while patients are alive. The primary analysis method has been investigated with extensive simulation studies and it has been confirmed that it keeps the alpha level and has good operating characteristics across a range of plausible scenarios. A small adjustment will be made to the nominal significance level and the critical value at the final analysis to take into account the interim analysis (see Section 9.5 for details). No adjustment to the sample size calculation is done for this.

9.2 Sample Size Determination

This is an event-driven study. The study is planned to last 42 months in total with a recruitment period of 24 months and participants are to be randomized 1:1 to finerenone and placebo. The sample size determination is based on a simulation study assuming a joint frailty model in order to account for the correlation between HF events and CV death, and to model participant heterogeneity with respect to baseline intensities/hazards. That is, given the participant-specific gamma distributed frailties, we assume a homogeneous Poisson process for HF events and an exponential distribution for the time to CV death. Furthermore, the frailty term is assumed to be the same for HF events and CV death.

The placebo rate parameter of the Poisson process and the hazard rate of the exponential distribution were first chosen as 0.014 HHFs/month per participant and 0.004 CV deaths/month per participant, respectively. These values lead to an observed annualized placebo rate of first composite events of 9.0 (events/ 100 participant-years) and an observed annualized placebo rate of CV death of 3.5. These observed rates are similar to rates observed in the literature, i.e. an annualized rate of first composite event of 9.1 was observed in the CHARM-Preserved trial, 8.9 was observed in PARAGON-HF and 8.5 in the BNP stratum of the TOPCAT trial. Regarding CV death, an annualized placebo rate of 3.9 per 100 participant-years was observed in CHARM-Preserved, 3.1 was observed in PARAGON-HF and 3.9 was also observed in the TOPCAT BNP stratum. Since it is planned to recruit more participants with a very recent hospitalization than in previous trials, which would be at a higher risk of events, the rate parameters were subsequently increased by 25% for CV death leading to a rate of 0.005125 CV deaths/ month per participant. For HF events, the rate was increased by 30% to 0.0182 HF events /month per participant to also account for the inclusion of urgent HF visits, which have not been included in primary endpoint of the former trials. The additional increase in event rate is in line with the increase reported for PARAGON-HF (Solomon et al. 2019), Supplementary Appendix). The resulting observed annualized placebo rates are then 12.5 for first composite events and 4.6 for CV death. The frailty variance is chosen as 5.0, so that the ratio of total composite to first composite events is about 1.8. Similar ratios have been observed across a number of heart failure studies (Anker and McMurray 2012). Non-CV deaths are simulated as exponentially distributed censoring events with a rate of 0.0016 non-CV deaths/month per participant, leading to approximately 70% of all deaths being due to CV causes.

As treatment effects, a hazard ratio for CV death of 0.8 and a rate ratio for heart failure events of 0.75 are assumed. With approximately 5500 randomized participants, it is expected to observe approximately 1310 first events and approximately 2375 total events leading to a power of 90% to show an effect at a two-sided alpha level of 5%. Under these assumptions it

is expected to observe a 19% decrease in the rate of the primary endpoint for finerenone. An annual drug discontinuation rate of 5% is assumed, with finerenone participants having the same risk of events as placebo participants after discontinuation and no change in event rate for discontinuing placebo participants. Participants discontinuing study intervention are expected to remain under observation in the study. Table 9–1 below shows the resulting power under deviations from the assumed treatment effect as well as the power for a time-to-first composite event analysis. As it would be desirable for a single pivotal trial to obtain a higher level of evidence so that the power at an alpha level of 1% is also given.

Table 9–1 Power for assumed sample size scenario and some variations

Sample size	Rate ratio HF events	Hazard ratio CV death	Power primary α=5%	Power primary α=1%	Power Time-to-first α=5%
5500	0.75	0.80	90%	74%	74%
	0.75	0.90	89%	73%	64%
	0.78	0.90	79%	58%	53%
	0.72	0.80	95%	86%	82%

Abbreviations: α = alpha; CV = cardiovascular; HF = heart failure

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Table 9–2 Populations for Analyses

Population	Description
Enrolled	All participants who sign the informed consent form (ICF).
Randomly assigned to study intervention	All participants randomly assigned to study intervention.
Safety analysis set (SAF)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Full analysis set (FAS)	All randomized participants. Participants will be analyzed according to the intervention they were randomized to. Only potential reasons for exclusion would be a clearly erroneously randomization, or major GCP violations, for example, a serious suspicion of fraud.

9.4 Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1 Efficacy Analyses

9.4.1.1 Primary Efficacy Variable

The primary efficacy variable is the composite endpoint of CV death and/or total (first and recurrent) events for HF. See Section 9.1 for a description of the primary analysis.

As part of the primary analysis, separate estimates of treatment effects for the components of the primary endpoint, total HF events and CV death, will be obtained. For this analysis, a joint frailty model will be used (Rogers et al. 2016). This model gives a treatment effect on total HF events which is adjusted for a potential treatment effect on CV death. An effect on CV death might otherwise dilute the effect seen on the hospitalizations, i.e. an effective treatment will prevent CV deaths especially in the more severely ill participants, which then potentially realize many hospitalizations. The joint frailty model will be fitted using the method described in the paper by (Liu and Huang 2008) where the unknown baseline hazard for CV death and unknown baseline intensity for HF events are approximated by piecewise constant functions. A gamma frailty distribution will be assumed. As a sensitivity analysis a joint frailty model with constant hazard and intensity functions will be fitted as well. The flexible model can sometimes have convergence issues, should this occur, the estimate of HF events treatment effect of the model with the constant baseline functions will be considered to be the main estimate. For CV death the main treatment effect estimate will be derived from a stratified Cox proportional hazards model for time to CV death and the main p-value from a stratified log-rank test, the estimate from the joint frailty model will be considered supportive.

Note that the study is not powered to show an effect on CV death alone. While this is the case, a sufficient number of deaths are expected so that an excess risk in mortality can be excluded. Under the assumptions of the sample size determination, approximately 535 CV deaths and approximately 775 all-cause deaths are expected to occur in the study. Even though no formal statistical tests for exclusion of an increased risk will be performed, these expected event counts would result in a relatively high power to exclude hazard ratios on all-cause mortality (ACM) above 1.15 and 1.25. Table 9–3 provides the respective power values under different assumed values for the true hazard ratio on CV death and assuming no treatment effect on non-CV deaths (HR_{NonCVD}=1.0). Similar to the primary endpoint, a treatment policy strategy is used for treatment discontinuation. With exclusion of a certain hazard ratio value it is meant that the upper limit of a 95%-confidence interval is below the value.

Table 9–3 Power to exclude increased hazard ratio on all-cause mortality under different assumed treatment effects on CV death

True HR_{CVD}	Exclude HR_{ACM} >1.15	Exclude HR_{ACM} >1.25
0.8	94%	>99%
0.9	78%	97%
1.0	52%	88%

Abbreviations: ACM = all-cause mortality; CV = cardiovascular; CVD = cardiovascular death; HR = hazard ratio;

As supportive analysis, stratified Cox proportional hazard regression analyses of time to first composite event (CV death or first HF event) as well as and time to first HF event will also be performed and Kaplan-Meier plots will be provided. An additional analysis of the primary endpoint will exclude urgent HF visits and consider only CV deaths and HHFs as events.

As a sensitivity analysis, the number of primary composite events will also be analyzed using a negative binomial regression model including stratification factors and treatment group as covariates and log follow-up time as an offset parameter.

A total-time approach considering times from randomization to the onset of first, second, third composite event using a (Prentice et al. 1981, Wei et al. 1981) model will be applied. This model enables analysis of the cumulative effect on the primary endpoint from randomization (i.e. the effect on second event includes the effect on the first, and the effect on third event includes the effects on the first and second). The corresponding individual hazard ratios with 95% CIs comparing treatment groups on the first, second, and third event will be presented. In addition a conditional gap-time model according to Prentice et al will be applied to obtain hazard ratio estimates with 95% CIs for the time from first to second and from second to third event (note that this gives a non-randomized comparison). Both models will employ robust standard errors and include the stratification factors and treatment group as fixed effects.

Additional supportive analyses will be considered and will be described in the SAP.

9.4.1.2 Secondary Efficacy Variables

Secondary efficacy variables are the following:

- Change from baseline to Month 6, 9 and 12 in TSS of the KCCQ
- Time to first occurrence of composite renal endpoint:
  sustained decrease in estimated glomerular filtration rate (eGFR) ≥40% relative to baseline over at least 4 weeks, or sustained eGFR decline <15ml/min/1.73m^2 or initiation of dialysis or renal transplantation.
- Time to all-cause mortality.

The secondary hypotheses will be formally tested and statistical inferences will be made only if the primary hypothesis is rejected. KCCQ and the composite renal endpoint will be tested hierarchically in this order. As a hard endpoint and objective indicator of benefit-risk, time to all-cause mortality will be tested at a full level of alpha, after the rejection of the primary hypothesis. The components of the primary endpoints, total HF events as well as CV death, will also be tested at the full level of alpha after the primary hypothesis is rejected. Testing of time-to-all-cause mortality and the components of the primary endpoint will thus be done outside of the alpha-preserving procedure for the primary and other secondary efficacy variables (KCCQ, renal composite).

The primary analysis of the secondary time-to-event variables will be done with a stratified log-rank test for testing and a stratified Cox proportional hazards model for obtaining a point estimate with 95% confidence interval. The Cox proportional hazards model will be stratified according to the stratification factors and include treatment group as fixed effect. Kaplan-Meier plots will be displayed and components of the composite renal endpoint will be analyzed.

The absolute change from baseline including measurements up to month 12 of the TSS of the KCCQ will be analyzed by a repeated measures mixed model including the factors treatment group, baseline, visit, baseline-by-visit interaction, and factors for the stratification levels. Differences between the finerenone and the placebo treatment groups will be calculated with two-sided 95% confidence intervals. The comparison assumes a common treatment effect across month 6, 9 and 12 and will be considered primary. This analysis will investigate the

effect on the TSS of the KCCQ while patients are alive and irrespective of any permanent treatment discontinuation. This means that all observed values will be included in the analysis without any specific imputation. A supportive analysis will apply a worst case imputation for death which means that if a patient dies, a worst score of 0 for the TSS will be imputed for all subsequent visits after the patient's death. Treatment effects at Month 6, 9 and 12 will also be investigated individually by adding a treatment-by-visit interaction into the model.

Events that could potentially fulfill the criteria for primary or secondary efficacy variables during the study will be evaluated by the CEC.

Definitions of individual endpoints (e.g. CV death) will be provided in the Endpoint Manual.

Additional supportive analyses will be considered and will be described in the SAP. The following subgroups will be considered in exploratory subgroup analyses for the primary and secondary efficacy variables. This will include descriptive statistics and a statistical test for interaction.

The randomization will be stratified by country/region and LVEF (<60%, ≥60%). The most important subgroups besides stratification factors are given below (with further details and subgroups provided in the SAP):

- Baseline serum potassium (≤4.5, >4.5 mmol/L)
- eGFR category at baseline (eGFR 25 to <45, 45 to <60, ≥60 mL/min/1.73 m²)
- Atrial fibrillation at baseline ECG (present, absent)
- Diabetes mellitus at baseline (present, absent)
- HHF (very recent [≤ 7 days from randomization], recent [>7d – 90 days], no index).

It is anticipated that in these proposed subgroups for analysis, differences in treatment effects may be observed according to the screening or baseline characteristics defined, due in part to the differences in the risk of clinical events expected in the different subgroups.

Furthermore, subgroup analysis usually required will be performed, including the following subgroups:

- Race
- Sex
- Age group.

9.4.1.3 Exploratory Variables

- Time to first CV hospitalization
- Time to first all-cause hospitalization
- Total number of CV hospitalizations
- Total number of all-cause hospitalizations
- Time to first occurrence of the following composite endpoint: CV death or non-fatal CV event (i.e. non-fatal myocardial infarction, non-fatal stroke, or HHF)
- Change in eGFR from baseline
- Days alive and out of hospital

- Time to new onset of atrial fibrillation
- Change in health-related quality of life summary scores from baseline measured by KCCQ and EQ-5D-5L
- Change from baseline in NYHA class.

Exploratory time-to-event variables will be analyzed using the stratified log-rank test and the stratified Cox proportional hazards model.

The absolute change of eGFR to baseline at each visit until Visit 10 (Month 24) will be analyzed by a mixed model with the factors treatment group, baseline eGFR, visit, treatment-by-visit interaction, baseline-by-visit interaction, and factors for the stratification levels (region and LVEF). Differences between the finerenone and placebo groups at each visit will be calculated, and corresponding two-sided 95% confidence intervals will be computed.

Frequency tables will be generated for the number and percentage of patients with a relative decrease in eGFR of ≥25%, ≥30%, ≥40%, ≥50% and ≥57% from baseline. The analysis will be performed for each visit and for any time post-baseline.

For each patient, the annual change in eGFR will be calculated by fitting the patient's eGFR assessments into a linear regression model with time as the independent variable. The derived annual change will be analyzed using an analysis of covariance (ANCOVA) model including baseline eGFR, treatment group and stratification factors as fixed effects.

Days alive and out of hospital (DAOH) will be summarized descriptively by treatment group; the percentage of DAOH with respect to total potential follow-up time as well as the number of days in hospital will also be provided. These analyses will be performed overall and separately by the stratification factors (region and LVEF).

DAOH will be analyzed by an ANCOVA model including potential follow-up time, treatment group, and stratification factors as fixed effects.

DAOH will be analyzed once considering the total potential follow-up time and once considering only the first year of follow-up.

For the KCCQ, 3 summary scores (symptom frequency score, total symptom score, and overall summary score) will be derived. For the KCCQ symptom frequency scores, the following will be presented by visit and treatment group: number of observations, number of missing values, minimum, first quartile, mean, standard deviation, median, third quartile, and maximum, including the changes from baseline.

For the EQ-5D-5L, summary scores will be calculated from the 5 dimensions according to the scoring instructions from Europe and the US (refer to the EQ-5D-5L User Guide (EuroQoL_Group 2013) and to the EQ-5D Value Sets (Szende et al. 2007). The values and the changes from baseline of the summary scores and the EuroQol Group visual analogue scale (EQ VAS) will be summarized by treatment group and visit using the same descriptive statistics as for the KCCQ.

9.4.2 Safety Analyses

All safety analyses will be performed on the SAF.

The following safety procedures and variables will be assessed during the study:

- SAEs and AEs leading to discontinuation of treatment with study intervention
- Change in body weight from baseline
- Change in serum potassium from baseline
- Number of participants with hyperkalemia (serum potassium ≥5.5 mmol/L)
- Number of participants with severe hyperkalemia (serum potassium ≥6.0 mmol/L)
- Number of participants with hospitalization for hyperkalemia
- Number of participants permanently discontinuing study intervention due to hyperkalemia
- Change in vital signs (heart rate, SBP and DBP) from baseline
- Change in renal function measured by eGFR (CKD-EPI formula) change from baseline
- Number of participants with hospitalization for worsening of renal function
- Number of participants permanently discontinuing study intervention due to worsening of renal function
- Changes in laboratory values from baseline.

An overall summary of all AEs and treatment emergent AEs (TEAEs) will be generated by treatment group.

The number and percentage of patients with TEAEs, post-treatment AEs occurring more than 3 days after last intake of study intervention, treatment-emergent SAEs, treatment-emergent study intervention-related AEs, treatment-emergent study intervention-related SAEs, TEAEs causing premature and permanent discontinuation of study intervention, treatment-emergent non-serious AEs, TEAEs by maximum intensity, drug-related TEAEs by maximum intensity will be summarized by treatment group using MedDRA terms grouped by Primary System Organ Class and Preferred Term.

The number of patients with treatment-emergent (until 3 days after last study intervention administration) abnormal laboratory values above or below the normal range will be tabulated by the laboratory parameter and treatment group.

Summary statistics including changes from baseline will be calculated by treatment group and visit for all quantitative laboratory parameters, i.e. for hematology, clinical chemistry and urinalysis. Geometric statistics and ratios to baseline will be presented for urinary albumin-to-creatinine ratio (UACR), creatinine, and NT-proBNP, instead of arithmetic statistics with changes from baseline. For eGFR the relative change will be displayed in addition to the absolute change from baseline.

Summary statistics for serum potassium, eGFR, and serum creatinine will also be repeated by treatment group and visit separately for each level of the stratification factors (region and LVEF).

The following special safety parameters will be further assessed by displaying the number and percentage of patients with safety events as described below by treatment group, visit, and for any time on treatment (including unscheduled assessments) and until 3 days after last study intervention administration. This will also be performed by stratification factors. The summaries will be provided for the number and percentage of patients with:

- Absolute value of serum potassium >5.0 mmol/L, ≥5.5 mmol/L and ≥6 mmol/L
- Relative decrease from baseline in eGFR of ≥25%, ≥30%, ≥40%, ≥50% and ≥57%
- Absolute value of eGFR <30 mL/min/1.73 m²
- Increase from baseline in serum creatinine >0.3 mg/dL and >0.5 mg/dL.

The percentage of patients with the respective events (non-stratified) at any time on treatment (including unscheduled assessments) and until 3 days after last study intervention administration will be compared between the finerenone and placebo groups by applying separate exploratory χ^2 tests with continuity correction. If the expected number of patients in at least 1 cell of the 2x2 contingency table is <5, Fisher's exact test will be applied instead of the χ^2 test. Estimates and two-sided 95% confidence intervals will be provided for each treatment group and the treatment differences. Clopper-Pearson confidence intervals will be calculated for each treatment group, while for treatment differences the exact unconditional confidence limits will be calculated.

9.5 Interim Analyses

One non-binding interim analysis for futility is planned when approximately 30% of the required total number of primary endpoint events have been observed.

The futility analysis is considered to be non-binding, the DMC will be asked to also consider important secondary efficacy endpoints as well as safety in their assessment.

In addition one formal interim analysis for efficacy is planned when approximately 2/3 of the required total number of primary endpoint events have been observed.

If the interim analysis shows clear and consistent benefit in the finerenone treatment group, the DMC may recommend early study termination. The Haybittle-Peto rule will be used to guide the decision regarding early stopping of the study for success: a reduction of 3 standard deviations (of the test statistic) in the analysis of the primary efficacy endpoint (two-sided p-value <0.0027) at the interim analysis. In addition, a nominal significant effect on CV death component should be present (two-sided p-value<0.05) at the interim analysis. Note: The criterion for CV death would not be considered to prove formal statistical significance, as it does not keep the alpha level. It has been added so that the trial is only stopped at the interim if there is at least a certain amount of evidence of a beneficial treatment effect on CV death.

The significance level of the final analysis, i.e. if the study doesn't stop for overwhelming efficacy at the interim analysis, will be adjusted accordingly in order to preserve the overall type I errror rate of 5%.

The Steering Committee will oversee and discuss with the sponsor overall blinded event rates to ensure that they are in line with protocol assumptions. If overall event rates are lower than expected, consideration will be given to altering the study design, such as increasing the sample size or extending the study duration without knowledge of any treatment effect.

The SAP will describe the planned interim analyses in greater detail.

9.6 Data Monitoring Committee (DMC)

Ongoing safety monitoring during the conduct of the study will be performed by an external and independent DMC. An independent statistical analysis center (SAC) will be involved in

processing unblinded safety data for the DMC. Analysis periods and procedures will be defined in an operational charter (DMC charter) filed in the study file.

Outcome events as defined in Section 8.3.6 will not be reported as AEs or SAEs by the investigators; however, they will be collected in the eCRF. The independent DMC will periodically review and assess all outcome events as well as safety data from the study for imbalances in safety outcomes in an unblinded manner. It is believed that in this way, patient safety can continue to be monitored throughout the duration of the trial, and the integrity of the study maintained. If unexpected safety issues are identified, specific amendments will be implemented based on the recommendation of the DMC.

Following data review, the DMC will provide written recommendations that will be transferred to the chairmen of the Steering Committee and Bayer. DMC opinions and recommendations will be notified by Bayer as soon as possible to the competent authorities and the IECs where they qualify for expedited reporting.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 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 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines:
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g. 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 amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Any substantial modification of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH Good Clinical Practice and national and international regulations.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements, ICH guidelines, the IRB/IEC, and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor 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 course of the study and for one year after completion of the study.

10.1.3 Informed Consent Process

The investigator or his/her qualified representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance

Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented 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 authorized representative.

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

10.1.4 Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor 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 his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees Structure

Clinical Event Committee (CEC)

The main task of the CEC, which is composed of a panel of experts in cardiology and nephrology, is to adjudicate all HHFs, HF equivalents and all deaths. The committee will be provided with all relevant documentation related to the event.

The procedures followed by the committee will be specified in the CEC charter. Adjudication results will be the basis for the final analysis.

Data Monitoring Committee (DMC)

Ongoing safety monitoring during the conduct of the study will be performed by an independent external and unblinded DMC (see Section 9.6). Analysis periods and procedures will be defined in the DMC charter and filed in the electronic trial master file. Following data review, the DMC will provide written recommendations that will be transferred to Bayer and the Steering Committee chair. All other definitions will be provided in the DMC charter.

10.1.6 Dissemination of Clinical Study Data

Result summaries of Bayer's sponsored clinical trials in drug development Phases 2, 3, and 4 and Phase 1 studies in participants are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "*Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases*". In addition, results of clinical drug

trials will be provided on the publicly funded website www.ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.

Bayer commits to sharing upon request from qualified scientific and medical researchers participant-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in participants for medicines and indications approved in the United States (US) and European Union (EU) on or after 01 JAN 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g. 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 provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g. Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized 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 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 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.
- The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this. It is the expectation of the sponsor that all data have source documentation available at the site.
- Data reported on the CRF or 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 can be found in ICH-GCP guidelines E6(R2) § 1.51, 1.52.

10.1.9 Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. 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 the sponsor or 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, the sponsor'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, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(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 subject and should assure appropriate subject therapy and/or follow-up.

10.1.10 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 the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual

site data. In this case, a coordinating investigator will be designated by mutual agreement.

- In addition, the sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10–1 will be performed by the central laboratory.
- In addition to samples for the central laboratory, other blood safety samples will be taken from the Screening Visit onwards for analysis at the local laboratory. These samples will be taken only as long as the participant has not prematurely and permanently discontinued study intervention.
- eGFR (CKD-EPI) (Horio et al. 2010, Levey et al. 2009) must be measured/calculated locally for as long as the participant is treated with the study intervention
- Up-titration or down-titration of the study intervention will be based on local potassium and must be documented in the eCRF. Down-titration of the study intervention will occur for safety reasons only.
- Potassium values should be recorded using a single decimal point (e.g. 4.5 mmol/L or mEq/L). In the event of hyperkalemia, please see Section 6.6.1 for guidance on treatment.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing. Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.

Table 10–1 Protocol-Required Clinical/Safety Laboratory Assessments

Parameter	Component
Hematology	White blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hb), hematocrit, platelets, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), red cell distribution width (RDW)
Clinical chemistry (full)	Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), creatinine kinase (CK), serum creatinine, eGFR (CKD-EPI (Horio et al. 2010, Levey et al. 2009), blood urea nitrogen, bilirubin (fractionated), sodium, serum potassium
Glycated hemoglobin	HbA1c
Urinalysis	Urinary albumin-to-creatinine ratio (UACR)
Biomarkers	N-terminal prohormone B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin-t (hs-TnT)

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.
- Events related to study-required procedures (e.g. invasive procedures, side effects caused by change of concomitant medication to fulfil study eligibility).

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy) that is not required by the study protocol as outlined by the SoA: the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or

convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

- The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE/SAE CRF pages.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated safety-relevant SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection transmission (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).
- Contacts for SAE reporting can be found in in the investigator site file.

SAE Reporting to the Sponsor via Paper CRF

- Email transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor.
- In rare circumstances and if email transmission is not feasible, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the investigator site file.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (e.g. mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female.
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

According to pre-clinical and clinical data, Finerenone does not indicate teratogenicity/ fetotoxicity in early pregnancy (please refer to the Investigator's Brochure for details). Based on these data, women of child-bearing potential can be included into the trial if reliable contraception is used.

Adequate contraception is defined as any combination of at least 2 effective methods of birth control. Highly effective birth control methods are hormonal contraception (progesterone only), combined hormonal contraception (estrogen and progesterone), intrauterine devices and

intrauterine hormone-releasing systems. One of these methods should be combined with a supplementary barrier method (preferably male condom) due to possible drug-to drug interactions which might reduce efficacy of the hormonal contraception. Contraception should be used until 30 days after last intake of study intervention.

Male participants do not have to use condoms in the study, because there is no indication of male-mediated developmental toxicity. Therefore, female partners of male participants are also not required to use contraception.

Collection of Pregnancy Information:

Male Participants with Partners who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, after obtaining the signed informed consent from both parents, unless local law or specific circumstances of the respective case allow otherwise, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
  - While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
  - A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.5 Appendix 5: Definitions of Clinical Events

General clinical event definitions are based on Hicks`s criteria (Hicks et al. 2018) of each component of the primary composite endpoint and can be found below. Further details of all endpoint definitions and its criteria will be provided in the Endpoint Manual and CEC Charter.

10.5.1 Heart Failure (HF) Events

HF events include HHF as well as urgent HF visits. All HF events are to be captured on the eCRF.

10.5.1.1 Heart Failure Hospitalization (HHF)

- An HHF is defined as an event in which the participant is admitted to the hospital with a primary diagnosis of HF. The length of stay is **at least 24h** (or a change in calendar date if the hospital admission and discharge times are unavailable). The participant exhibits new or worsening symptoms of HF on presentation, has objective evidence of new or worsening HF (physical examination findings and/or laboratory criterion) and receives initiation or intensification of treatment specifically for HF.

10.5.1.2 Urgent Heart Failure (HF) Visits

- An urgent HF visit is defined as an event in which the participant has an urgent, unscheduled office/practice or Emergency Room visit for a primary diagnosis of HF, but not meeting the criteria for a HHF. The participant is not admitted to the hospital and exhibits new or worsening symptoms of HF (physical examination findings and/or laboratory criterion) and receives initiation of intravenous diuretic or vasoactive agent or mechanical or surgical intervention (see Endpoint Manual for details). Of note, significant augmentation of oral diuretic therapy will NOT be enough to fulfill the urgent HF visit criteria
- General consideration (urgent HF visits): Clinic visits for **scheduled** administration of HF therapies or procedures (e.g. intravenous diuretics, intravenous vasoactive agents or mechanical fluid removal) do NOT qualify as non-hospitalized HF events.

10.5.2 Cardiovascular (CV) Death

CV death includes any death resulting from an acute myocardial infarction, sudden cardiac death, sudden death, death due to HF, death due to stroke, death due to CV procedures, death due to CV hemorrhage, and death due to other CV causes.

10.6 Appendix 6: Country-specific Requirements

Country-specific requirements will be outlined in local amendments.

10.7 Appendix 7: Calculating the Child Pugh score

The severity of liver disease (Table 10–2) will determine the Child Pugh score (Table 10–3).

Table 10–2 Grading of severity of liver disease, adapted from (Pugh et al. 1973)

Factor	+1	+2	+3
Bilirubin (mg/dL)	< 2	2 – 3	> 3
Albumin (g/dL)	> 3.5	2.8 – 3.5	< 2.8
International Normalized Ratio	< 1.7	1.7 – 2.3	> 2.3
Ascites	None	Mild	Moderate / Severe
Encephalopathy	None	Grade I - II	Grade III – IV

Table 10–3 Classification using the added score from Table 10–2, adapted from (Pugh et al. 1973)

Child-Pugh Class	A	B	C
Points	5 – 6	7 – 9	10 – 15

10.8 Appendix 8: Abbreviations

ACC/AHA	American College of Cardiology/American Heart Association
ACEI	angiotensin-converting enzyme inhibitor
AE	adverse event
ALDO-DHF	Aldosterone Receptor Blockade in Diastolic Heart Failure
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	alkaline phosphatase
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
ARTS	Mineralocorticoid Receptor Antagonist Tolerability Study
ARTS-DN	Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy
ARTS-HF	Mineralocorticoid Receptor Antagonist Tolerability Study–Heart Failure
AST	aspartate aminotransferase
AUC	area-under-the-curve
BCRP	Breast Cancer Resistance Protein
BMI	body mass index
BNP	B-type natriuretic peptide
CEC	Clinical Event Committee
CFR	Code of Federal Regulations
CHARM	Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity
CHARMPreserved	Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity
CHF	chronic heart failure
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CV	cardiovascular
CVD	cardiovascular death
CYP3A4	cytochrome P450 isoenzyme 3A4
DAOH	days alive and out of hospital
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EPHESUS	Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
ESC	European Society of Cardiology

EOS	end-of-study (visit)
EQ-5D-5L	EuroQol Group 5-dimension, 5-level questionnaire
EQ VAS	EuroQol visual analogue scale
EU	European Union
EuroQoL	European Quality of Life (scale)
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GWTG-HF	Get With the Guidelines - Heart Failure
HbA1c	glycated hemoglobin
HF	heart failure
HFmrEF	HF with mid-range EF
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced EF
HHF	hospitalization for heart failure
HR	hazard ratio
HRT	hormone replacement therapy
hs-TnT	high-senstivity troponin-t
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IR	immediate release
IV	intravenous
IxRS	interactive voice / web response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAA	left atrial area
LAD	left atrial diameter
LAVI	left atrial volume index
LDL	low density lipoprotein
LVEF	left ventricular ejection fraction
LVMI	left ventricular mass index
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MR	mineralocorticoid receptor
MRA	mineralocorticoid receptor antagonist
NONMEM	non-linear mixed effect modeling

NSAID	non-steroidal anti-inflammatory drug
NP	natriuretic peptide
NT-proBNP	n-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
OATP	Organic Anion Transporter Polypeptide
OD	once daily
PARAGON-HF	Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction
PD	premature discontinuation
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetics
PT	post-treatment (visit)
RAAM-pEF	Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction
RAAS	renin-angiotensin aldosterone system
RALES	Randomized Aldactone Evaluation Study
RAVE	electronic data capturing system
RDW	red cell distribution width
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial
TSS	Total Symptom Score
UACR	urinary albumin-to-creatinine ratio
US(A)	United States (of America)
WOCBP	women of child-bearing potential
6MWT	6-minute walk test

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Title Page

Protocol Title: A multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of finerenone on morbidity and mortality in participants with heart failure (NYHA II-IV) and left ventricular ejection fraction ≥40% (LVEF ≥40%)

Protocol Number: 20103

Protocol Version: 3.0

Amendment Number: 2

Amendment Scope: Global

Compound Number: Finerenone / BAY 94-8862

Study Phase: 3

Short Title: Efficacy and safety of finerenone in participants with symptomatic heart failure and left ventricular ejection fraction ≥40% (LVEF ≥40%).

Acronym: **FINEARTS-HF** (**FIN**erenone trial to investigate **E**fficacy and s**A**fety superio**R** to placebo in pa**T**ient**S** with **H**eart **F**ailure)

Sponsor Name: Non-US: Bayer AG

US territory: Bayer Healthcare Pharmaceuticals Inc

Legal Registered Address: Non-US: Bayer AG, 51368 Leverkusen, Germany

US territory: 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA

Regulatory Agency Identifier Number(s): EudraCT 2020-000306-29

Protocol Date: 16 MAY 2022

The Medical Monitor's name and contact information will be provided separately.

Name: PPD PPD Role: PPD

This is an electronically generated document that does not bear any sponsor signatures. The signature of the sponsor's medically responsible person is filed in the TMF and available on request.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	16 MAY 2022
Amendment IND-2	13 JUL 2021
Amendment JPN-2	13 JUL 2021
Amendment CHN-2	23 FEB 2021
Amendment IND-1	21 DEC 2020
Amendment LTU-1	15 DEC 2020
Amendment 1	21 SEP 2020
Amendment USA-1	21 JUL 2020
Amendment SVK-1	03 JUL 2020
Amendment GBR-1	27 MAY 2020
Amendment JPN-1	06 APR 2020
Amendment CHN-1	24 MAR 2020
Original Protocol	05 MAR 2020

Amendment 2 (16 MAY 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This amendment was made to alter certain efficacy endpoints of the study. In addition, more clarity has been provided and inconsistencies were corrected.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 2.1 Study Rationale Section 3 Objectives and Endpoints Section 6.6.2 Monitoring of Renal Function and Dose Adjustment Section 9.4.1.2 Secondary Efficacy Variables	Change in the percentage decrease (from 40% to 50%) of the eGFR component of the secondary renal composite endpoint.	Based on updated finerenone data on FIGARO and FIDELIO studies.
Section 1.3 Schedule of Activities (SoA) Section 10.2 Appendix 2: Clinical Laboratory Tests	Removal of measurement of SARS-CoV-2 serology.	To reflect actual moment of pandemic. The mass vaccination made these measurements inaccurate.
Section 1.3 Schedule of Activities (SoA) Section 6.1 Study Intervention(s) Administered	Full unscheduled safety check for reasons other than hyperkalemia; otherwise only potassium to be rechecked	For clarity
Section 1.3 Schedule of Activities (SoA)	Addition of starting point (after last intake) for countdown to the PD Visit.	For clarity.
Section 1.3 Schedule of Activities (SoA)	Footnote s was added stating that at Visit 4 an additional NT-proBNP measurement from serum will be performed.	To accommodate the regulatory need for comparing adult biomarkers as a reference for measurement in the pediatric population.
Section 2 Introduction Section 7.1 Discontinuation of Study Intervention	Details of MRA and its effects adjusted. Addition of maximum permissible duration of MRA use.	To reflect current status of MRA use.

Section 1.1 Synopsis Section 2.1 Study Rationale Section 3 Objectives and Endpoints Section 9.4.1.1 Primary Efficacy Variable Section 9.4.1.2 Secondary Efficacy Variables Section 9.4.1.3 Exploratory Variables	Change in NYHA class from baseline was removed from exploratory endpoints, and time to total HF events and improvement in NYHA class from baseline to month 12 as secondary endpoints, and included analysis methods for these endpoints.	The endpoint was elevated to a key secondary endpoint given its meaningful clinical significance.
Section 3 Objectives and Endpoints Section 9.4.1.3 Exploratory Variables	Change in UACR from baseline, and time to first occurrence of the following composite endpoint: sustained decrease in eGFR ≥57% relative to baseline over at least 4 weeks, or sustained eGFR decline <15 ml/min/1.73m^2 or initiation of dialysis or renal transplantation, were added as exploratory endpoints.	These exploratory endpoints were added to compare with existing data from FIGARO and FIDELIO.
Section 5.1 Inclusion Criteria	Addition of details on NT-proBNP in relation to paroxysmal atrial fibrillation.	To reflect current guidance.
Section 5.2 Exclusion Criteria	It was clarified for Exclusion Criteria 8 and 18 that the laboratory parameters are only needed at screening if there is a suspicion of anemia or hepatic insufficiency.	Recommendation to clarify these criteria following local inspection in Argentina (The National Administration of Drugs, Foods and Medical Devices)
Section 5.2 Exclusion Criteria Section 6.5 Prior and Concomitant Therapy	Use of all moderate CYP3A4 inhibitors is allowed, whereas use of moderate CYP3A4 inducers is prohibited.	To reflect current label requirements. In addition, current FINEARTS-HF blinded interim data suggest that the use of 40 mg is safe in heart failure patients and no excess in AEs, in particular hyperkalemia or discontinuations was observed so far. Moreover, analyses of FIDELIO-DKD data show that serum potassium guided dose titration is the key factor managing serum potassium and preventing increased hyperkalemia at higher finerenone exposure levels and doses. An updated list of the most common CYP3A4 inhibitors will be provided separately outside of the protocol.
Section 5.4 Screen Failures	Re-screening allowed in exceptional circumstances (e.g. pandemic-related disruption).	To account for logistic issues.

Section 6.5 Prior and Concomitant Therapy	- Updated information on existing treatment showing mortality or morbidity benefit in participants with HFpEF. - Deletion of text on BCRP/OATP. - Sentence urging for caution while using acetylsalicylic acid at doses greater than 500mg a day was removed	- Updating to reflect recent data from EMPEROR-Preserved study in HFpEF - To reflect recently completed study (#21429) findings that showed an absence of any relevant effect of finerenone on BCRP/OATP. - Updated in accordance with the current label
Section 6.6.1 Monitoring of Blood Potassium and Dose Adjustment	Adjustment of description, requiring that potassium is retested if a patient was down-titrated or if study drug was interrupted.	Included for clarity.
Section 6.6.2 Monitoring of Renal Function and Dose Adjustment	Wording edited: re-test at central laboratory after 4 weeks to confirm eGFR decrease of <u>either</u> ≥50 % <u>or ≥57%</u>	50% is in line with the new secondary composite endpoint. 57% was added to compare with existing data from FIGARO and FIDELIO.
Section 7.1 Discontinuation of Study Intervention	Telephone consultation permitted, only if onsite EOS visit is not feasible.	To ensure the minimum required data collection in case subject is not able to visit the site.
Section 7.1 Discontinuation of Study Intervention Section 7.1.1 Temporary Discontinuation	Addition of conditions allowing the resumption of study intervention.	Restart of study intervention allowed if reason for permanent discontinuation changed and the investigator considers restart in the best interest of the subject.
Section 8.2.3 Clinical Safety Laboratory Assessments	Option to down-titrate in exceptional circumstances (e.g. supply issue).	To ensure continuation of treatment as far as possible in exceptional circumstances.
Section 8.3.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs	Addition of specific conditions of disease-related event: worsening of renal function.	Included for completeness
Section 8.8 Biomarkers	The biomarkers NT-proBNP and hs-TnT will be determined ~~in plasma~~ at the time points indicated in SoA for central laboratory assessments (Section 1.3).	To allow NT-proBNP to be measured in serum.
Section 9.1 Statistical Hypotheses	Analysis of the competing event of non-CV death and clarification for mean cumulative function were included	Included for clarity on handling and presentation of competing events.
Section 9.4.1.1 Primary Efficacy Variable	Included analysis and presentation of cumulative incidence function for the competing event of non-CV death. Clarified that cumulative incidence functions will use Aalen-Johansen estimates as opposed to Kaplan-Meier.	Clarity on handling and presentation of competing events
Section 9.4.1.2 Secondary Efficacy Variables	For the composite renal endpoint, included analysis and presentation of cumulative incidence function for the competing event of death. Clarified that cumulative incidence functions will use Aalen-Johansen estimates as opposed to Kaplan-Meier.	Clarity on handling and presentation of competing events

Section 9.4.1.3 Exploratory Variables	Added Mean rate of change in eGFR as measured by total eGFR slope and its subcomponents acute and chronic slope as an exploratory endpoint, and included analysis method for this endpoint.	New exploratory endpoint of eGFR slope was added, and detailed slope analysis will be based on new exploratory endpoint.
Section 9.4.1.3 Exploratory Variables	Updated proposed presentation of DAOH	Clarity on handling of interim analyses
Section 9.5 Interim Analysis	Added description of how the interim analyses will be conducted	Clarity on handling of interim analyses
Section 10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	WOCBP should use effective contraception. Table including contraceptives during the study was included for clarity.	Updated based on the current data available for finerenone.

In addition, corrections of errors, editorial and administrative changes have been made throughout the document that are not listed in this table.

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of finerenone on morbidity and mortality in participants with heart failure (NYHA II-IV) and left ventricular ejection fraction ≥40% (LVEF ≥40%).

Short Title: Efficacy and safety of finerenone in participants with symptomatic heart failure and left ventricular ejection fraction ≥40% (LVEF ≥40%).

Rationale: Study 20103 will be the first large-scale, long-term outcome study investigating the efficacy and safety of the non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone on morbidity and mortality in participants with heart failure (NYHA II-IV) and LVEF ≥40%.

An inappropriate release of aldosterone contributes to target organ damage found in heart failure (HF), myocardial infarction, chronic renal failure, and hypertension. The extensive expression of the mineralocorticoid receptor (MR) in the cardiovascular (CV) and renal systems, including myocytes, endothelial cells, vascular smooth muscle cells, and kidney mesangial cells, provides further evidence for the role of aldosterone in CV and renal injury.

Blockade of the action of aldosterone and potentially other MR ligands such as cortisol has been demonstrated to be of benefit in HF (Pitt et al. 1999, Zannad et al. 2010). Results from a short-term Phase 2b study (ARTS-HF Study 14564) reported a trend towards improvement of mortality and CV morbidity with finerenone treatment in addition to standard therapy for HF (Filippatos et al. 2016); however, long-term conclusive outcome studies examining whether MRAs can prevent CV events are still lacking in this patient population. Study 20103 will be the first study to address these questions in this population.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
1. To demonstrate the superiority of finerenone to placebo in reducing the rate of the composite CV endpoint.	Composite primary endpoint: • Cardiovascular (CV) death and total (first and recurrent) heart failure (HF) events (hospitalizations for heart failure [HHF] or urgent HF visits) in HF patients (New York Heart Association [NYHA] class II–IV) and LVEF ≥40%.
Secondary	
2. To determine the superiority of finerenone to placebo for each secondary endpoint 3. To assess the safety and tolerability of finerenone	Secondary endpoints: • Time to total (first and recurrent) HF events • Improvement in NYHA class from Baseline to Month 12 • Change from baseline to Month 6, 9 and 12 in Total Symptom Score (TSS) of the KCCQ • Time to first occurrence of composite renal endpoint: sustained decrease in estimated glomerular filtration rate (eGFR) ≥50% relative to baseline over at least 4 weeks, or sustained eGFR decline to <15 ml/min/1.73m^2 or initiation of dialysis or renal transplantation. • Time to all-cause mortality

Overall Design: Multicenter, randomized, double-blind, parallel-group, placebo-controlled

Intervention Model: Parallel-group assignment.

Primary Purpose: Treatment.

Number of Arms: 2

Masking:
- Sponsor
- Participant
- Care provider
- Investigator
- Outcomes assessor

Number of Participants: Approximately 6900 participants will be screened to achieve approximately 5500 randomly assigned to study intervention.

Intervention Groups and Duration:

Recruitment is expected to last for approximately 24 months. Randomization will take place within 2 weeks of screening. Eligible participants will be randomized in a 1:1 ratio to receive once daily (OD) treatment with finerenone or placebo. Planned treatment duration is approximately 18 to 42 months until expected events are reported. For participants still taking study intervention when the end of study is reached, the post-treatment follow-up period will last for 30 (+5) days and will end upon completion of the post-treatment (PT) phone call.

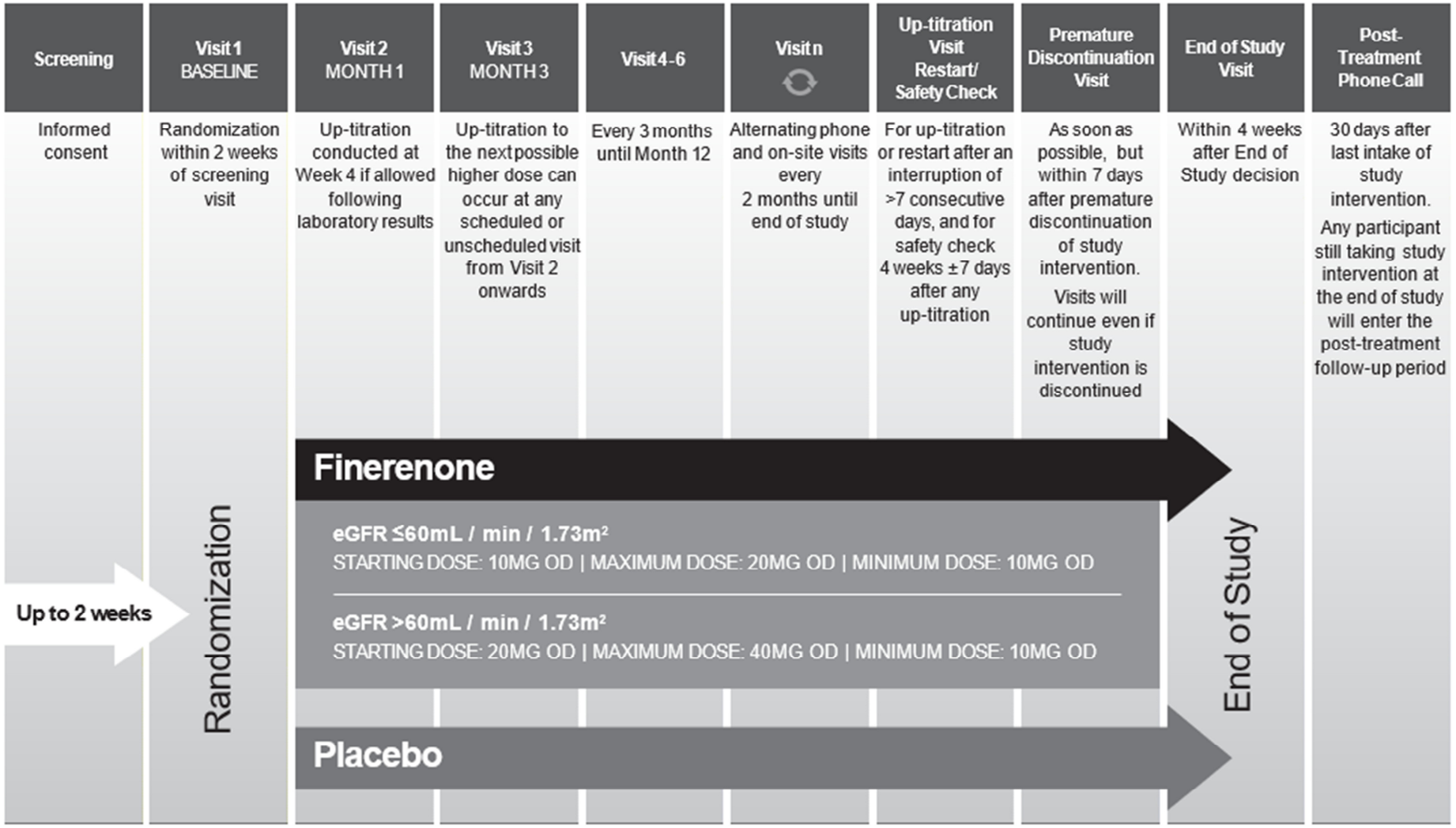
The starting dose will depend on the participant's eGFR level at the Baseline Visit: participants with an eGFR ≤60 mL/min/1.73m² will start with 10 mg OD (dose level 1) and have a maximum maintenance dose of 20 mg OD (dose level 2), whereas participants with an eGFR >60 mL/min/1.73m² will start with 20 mg OD (dose level 2) and have a maximum maintenance dose of 40 mg OD (dose level 3). The minimum dose level is 10 mg for all participants. Medication intake is OD preferably in the morning.

Provided the participant's safety is not affected, and if considered appropriate by the investigator, the participant should be up-titrated to the next higher dose level ideally after 4 weeks of treatment, with the goal of keeping the participant on the maximum tolerated dose level for as long as possible. At any scheduled or unscheduled visit from Visit 2 (Month 1) onwards, up-titration to the next possible higher dose should be based on the level of serum/plasma potassium and eGFR. Participants will attend an additional safety visit 4 weeks ± 7 days after each up-titration. Down-titration or interruption of study intervention is allowed at any time during the study for safety reasons.

Concomitant therapy is best medical care to treat comorbidities at the investigator's discretion.

Data Monitoring Committee: Yes.

1.2 Schema


Screening
Visit 1 BASELINE
Visit 2 MONTH 1
Visit 3 MONTH 3
Visit 4-6
Visit n
Up-titration Visit Restart/ Safety Check
Premature Discontinuation Visit
End of Study Visit
Post-Treatment Phone Call
Informed consent
Randomization within 2 weeks of screening visit
Up-titration conducted at Week 4 if allowed following laboratory results
Up-titration to the next possible higher dose can occur at any scheduled or unscheduled visit from Visit 2 onwards
Every 3 months until Month 12
Alternating phone and on-site visits every 2 months until end of study
For up-titration or restart after an interruption of >7 consecutive days, and for safety check 4 weeks ±7 days after any up-titration
As soon as possible, but within 7 days after premature discontinuation of study intervention.
Visits will continue even if study intervention is discontinued
Within 4 weeks after End of Study decision
30 days after last intake of study intervention.
Any participant still taking study intervention at the end of study will enter the post-treatment follow-up period
Up to 2 weeks
Randomization
Finerenone
eGFR ≤60mL / min / 1.73m²
STARTING DOSE: 10MG OD | MAXIMUM DOSE: 20MG OD | MINIMUM DOSE: 10MG OD
eGFR >60mL / min / 1.73m²
STARTING DOSE: 20MG OD | MAXIMUM DOSE: 40MG OD | MINIMUM DOSE: 10MG OD
Placebo
End of Study

1.3 Schedule of Activities (SoA)

The schedule of activities (SoA) is displayed for the study as a whole in Figure 1–1 (‘*Main SoA*’) and for participants who prematurely discontinue the study, minimal assessments will need to be performed as outlined in Figure 1–2 (‘*Premature Discontinuation SoA*’).

Figure 1–1 Main SoA

Visit Number / Name	**Screening [a]**	**Baseline [a] 1**	**2**	**3**	**4**	**5**	**6**	**7, 9, 11, 13, 15, 17, 19, 21 etc.[b]**	**8, 12, 16, 20 etc.**	**10, 14, 18 etc.**	**Up-titration, re-start and safety check [c]**	**PD Visit [d]**	**EOS Visit [e]**	**PT Visit [f]**
Day (D) / Month (M)		**D1**	**M1**	**M3**	**M6**	**M9**	**M12**	**M14 and every 4 months (i.e. M18, M22, M26, M30, M34, M38, M42 etc.)**	**M16 and every 8 months (i.e. M24, M32, M40 etc.)**	**M20 and every 8 months (i.e. M28, M36 etc.)**				
Visit window (days)		**-**	**±3**	**±3**	**±6**	**±6**	**±6**	**±7**	**±7**	**±7**	**±7**			**+5**
On-site (O)/Tel. contact (☎)	**O**	**O**	**O**	**O**	**O**	**O**	**O**	**☎**	**O**	**O**	**O**	**O**	**O**	**☎**
Initiation procedures														
Informed consent	X													
Demographic data	X													
Substance use (alcohol & tobacco)		X												
Medical history	X													
NYHA class assessment	X	X	X	X	X	X	X	X	X	X		X	X	X
Prior and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
In- and exclusion criteria	X	X												
Clinical procedures/ assessments														
Weight	X	X	X	X	X	X	X		X	X	X	X	X	
Height	X													
Waist and hip circumference	X													
Vital signs [g]	X	X	X	X	X	X	X		X	X	X	X	X	
12-lead ECG (local)		X												
AE and endpoint assessment (renal endpoints require additional confirmed creatinine measurement; see Table 6–3 for details)		X	X	X	X	X	X	X	X	X	X	X	X	X
Study intervention														
Randomization (IxRS)		X												
Dispense study intervention		X	X	X	X	X	X		X	X	X[r]			

Figure 1–1 Main SoA

Visit Number / Name	Screening [a]	Baseline [a] 1	2	3	4	5	6	7, 9, 11, 13, 15, 17, 19, 21 etc.[b]	8, 12, 16, 20 etc.	10, 14, 18 etc.	Up-titration, re-start and safety check [c]	PD Visit [d]	EOS Visit [e]	PT Visit [f]
Day (D) / Month (M)		D1	M1	M3	M6	M9	M12	M14 and every 4 months (i.e. M18, M22, M26, M30, M34, M38, M42 etc.)	M16 and every 8 months (i.e. M24, M32, M40 etc.)	M20 and every 8 months (i.e. M28, M36 etc.)				
Visit window (days)		-	±3	±3	±6	±6	±6	±7	±7	±7	±7			+5
On-site (O)/Tel. contact (☎)	O	O	O	O	O	O	O	☎	O	O	O	O	O	☎
Provide and review the study contact card		X					X			X				
Administration of study intervention at study site		X		X										
Administration of study intervention before the visit			X		X	X	X		X	X				
Study intervention accountability			X	X	X	X	X		X	X	X	X	X	
Local/central laboratory														
Local laboratory [h] (potassium and creatinine [i])	X [j]	X [j, m]	X [k]	X [k]	X [k]	X [k]	X [k]		X [k]	X [k]	X [k]	X [k]	X [k]	
Pregnancy test	X [L]	X [L, m]												
Central laboratory including urinalysis (see Table 10–1)		X [m]	X	X	X [s]	X	X		X	X		X	X	
Biomarkers NT-proBNP and hs-TnT		X [m]		X			X							
Exploratory biomarkers		X [m]		X			X						X	
Pharmacokinetics				X [n]			X [o]			X [o]				
Other study procedures														
KCCQ [q]		X			X	X	X		X			X	X	
EQ-5D-5L [q]		X			X	X	X		X			X	X	
PGIC (applicable to selected sites only) [q]					X	X	X							
PGIS (applicable to selected sites only) [q]		X			X	X	X							

Please note that footnotes to both SoAs can be found below Figure 1–2.

Figure 1–2 Premature Discontinuation SoA

Visit Number / Name		**2**	**3**	**4**	**5**	**6**	**7, 9, 11, 13, etc.[b]**	**8, 12, 16, 20 etc.**	**10, 14, 18 etc.**	**EOS Visit [e]**
Day (D) / Month (M)		**M1**	**M3**	**M6**	**M9**	**M12**	**M14 every 4 months (i.e. M18, M22 etc.)**	**M16 every 8 months (i.e. M24, M32, M40 etc.)**	**M20 every 8 months (i.e. M28, M36 etc.)**	
Visit window (days)		**±3**	**±3**	**±6**	**±6**	**±6**	**±7**	**±7**	**±7**	
On-site (O)/Tel. contact (☎)		**☎**	**O**	**O**	**☎**	**O**	**☎**	**O**	**O**	**O**
Central laboratory (eGFR)	**Premature discontinuation [p]**		X	X		X		X	X	X
Biomarkers NT-proBNP and hs-TnT			X			X				
AE and endpoint assessment (renal endpoints require additional confirmed creatinine measurement; see Table 6–3 for details)		X	X	X	X	X	X	X	X	X
Concomitant medication		X	X	X	X	X	X	X	X	X
KCCQ [q]				X		X		X		X
EQ-5D-5L [q]				X		X		X		X

Please note:

- 1 month corresponds to 30 days
- Study visits should occur as close as possible to the specified time points in the protocol, but time windows are permitted as specified in the SoA
- At any scheduled or unscheduled visit, the dose of study intervention may be increased to the next possible higher dose, based on serum/plasma potassium level analyzed in the local laboratory and provided the participant was already on a stable dose for 4 weeks ±7 days.

Abbreviations: AE = adverse event; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; D = Day; eGFR = estimated glomerular filtration rate; ECG = electrocardiogram; EOS = end-of-study; EQ-5D-5L = EuroQoL Group 5-dimension 5-level questionnaire; hs-TnT = high-sensitivity troponin-t; IxRS = interactive voice / web response system; med. = medication; KCCQ = Kansas City Cardiomyopathy Questionnaire; M = Month; NT-proBNP = n-terminal prohormone B-type natriuretic peptide; NYHA = New York Heart Association; O = on-site; PGIC = Patient Global Impression of Change; PGIS = PGI of Severity; PD = premature discontinuation; PT = post-treatment; SoA = schedule of activities; Tel. = telephone

a Randomization has to occur within 2 weeks of the Screening Visit. If the Screening Visit and Visit 1 (Day 1, Baseline) are performed on the same day, procedures listed for both visits are to be performed only once.

b Study visits to be conducted as a clinic visit or a telephone contact visit. These visits will alternate at 4-monthly intervals from Month 12 onwards with participant contact being made every 2 months.

c This visit should be performed for safety check after any up-titration (4 weeks ±7days) and after restart of study intervention following an interruption for >7 consecutive days. A full unscheduled safety visit should be performed within an adequate timeframe proposed by the investigator after down-titration for reasons other than hyperkalaemia, otherwise only potassium is to be rechecked (refer to Table 6–1)

d The PD Visit should take place as soon as possible but within 7 days after the last intake of study intervention. If the PD Visit cannot be performed within the timeframe specified, no PD Visit is required. All randomized participants will be followed until the study ends, even if they did not take study intervention or permanently discontinued study intervention.

e After the study site is notified of end of study decision, an EOS Visit should be scheduled as soon as possible (but within 4 weeks at the latest).

f For all participants still on treatment with study drug at the EOS Visit, the post-treatment (PT) telephone call (☎) has to be performed 30 days +5 days after the last intake of study drug.

g For vital sign collection, please adhere to instructions in Section 8.2.2.

h If BNP, NT-proBNP values (related to inclusion criteria) are not available in medical records, use values assessed by local laboratory.

i Creatinine will be used to calculate eGFR using CKD-EPI (Horio et al. 2010, Levey et al. 2009)

j If local laboratory data for potassium and eGFR are available within the last 24 hours, these may be used instead. This also applies when screening and baseline visits are not combined.

k Study participants may have their local laboratory assessments taken up to 3 days prior to the study visit.

L Female participants of childbearing potential must have a negative serum or urine pregnancy test at screening and baseline. Further serum or urine pregnancy tests should be performed in participants of childbearing potential as required by national/institutional regulations (e.g. at every visit). At any time during study participation, additional pregnancy testing should be performed upon suspicion of pregnancy.

m All procedures at Visit 1 are to be performed prior to randomization.

n One trough sample is to be collected at steady state before study intervention intake at Visit 3 (if not possible e.g. because study intervention was taken at home before the visit, the trough sample collection can be postponed to Visit 4 or 5); study intervention is to be administered at the study site at this visit.

o Sample to be taken during the visit 1.5-10 hours after study intervention intake at home.

p The procedures/assessments to be performed at the PD Visit are listed in the main SoA (Figure 1–1). After completing the PD Visit, all subsequent visits are to be performed according to the Premature Discontinuation SoA (Figure 1–2). Any visits performed prior to the PD Visit do not need to be repeated (e.g. if PD is at Visit 5, there is no need to repeat previous visits).

q Questionnaires are to be completed by the participants before conducting any study procedure. See also Sections 8.1.1, 8.1.2 and 8.1.3 for details**.**

r Only if applicable**.**

s At Visit 4 an additional NT-proBNP measurement from serum will be performed**.**

2. Introduction

Heart failure (HF) is usually a chronic progressive disease characterized by intermittent acute exacerbations. The underlying cause is usually a reduction in the ability of the heart to contract (systole) and/or fill (diastole) effectively.

HF is a leading cause of CV morbidity and mortality (Chen et al. 2011). Approximately 1-2% of the adult population in developed countries has HF, with the prevalence rising to ≥10% among persons 70 years of age or older (Mosterd and Hoes 2007). Projections in the US show that the prevalence of HF will increase by 46% from 2012 to 2030, resulting in >8 million people with HF (1 in every 33) in the US (Heidenreich et al. 2013). Similar results were found in selected western European countries (Danielsen et al. 2017).

Epidemiological studies have reported that about 50% of patients with HF have a relatively normal or slightly reduced left ventricular ejection fraction (LVEF), in the range of 40% and above, also referred to as HF with preserved ejection fraction (HFpEF) (Fonarow et al. 2007, Hogg et al. 2004, Owan et al. 2006, Swedberg et al. 1999, Yancy et al. 2006).

HFpEF is caused by a complex interplay of multiple impairments in ventricular diastolic and systolic reserve function, heart rate reserve and rhythm, atrial dysfunction, stiffening of the ventricles and vasculature, metabolic derangements, coronary microvascular dysfunction with impaired vasodilatation, pulmonary hypertension, endothelial dysfunction, and abnormalities in the periphery, including skeletal muscle (Borlaug 2014).

The ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure from 2016 identified patients with LVEF that ranges from 40 to 49% as a separate group and introduced a new term '*HF with mid-range ejection fraction (HFmrEF)*'.

When compared with HFrEF patients, patients with HFpEF are predominantly elderly, more women are affected and occurrence of comorbidities such as arterial hypertension and atrial fibrillation are higher in the HFpEF population whereas the occurrence of coronary artery disease was less likely (Bhatia et al. 2006, Fonarow et al. 2007, Martinez-Selles et al. 2012, Owan et al. 2006, Vaduganathan et al. 2016, Yancy et al. 2006).

As the population ages, the prevalence of diabetes mellitus, obesity and hypertension increases, the substrate for developing HF, in particular HFpEF, and its incidence will therefore increase dramatically in the coming decades (Owan et al. 2006). With the increased longevity in western societies, the enormous public-health problem of HFpEF will continue to grow. In this context, data from Get With The Guidelines–Heart Failure (GWTG-HF), a very large, nationwide study of HF hospitalization in the US (n >110,000) showed that the proportion of patients hospitalized with HF who had HFpEF increased from 33% in 2005 to 39% in 2010. Within the same time interval, the proportion of HHF due to HFrEF decreased from 52% to 47% (Steinberg et al. 2012).

HHF strongly predicts a poor prognosis: in patients with HFpEF the rates of mortality and re-admission at 60 to 90 days after discharge are as high as 9.5% and 29.2%, respectively and comparable as to the rates in HFrEF, being 9.8% and 29.9%, respectively. In hospital mortality was lower in HFpEF patients although the difference was small (Fonarow et al. 2007, Owan et al. 2006). HHF is the predominant cause of hospitalization in HFpEF patients representing a potential target in order to modify prognosis and quality of life.

To date, international guidelines acknowledge a lack of evidence in the management of HFpEF patients, as no treatment has yet been shown to reduce morbidity and mortality in

patients with HFpEF. Therefore, management is limited to guideline-based optimal treatment of comorbidities as arterial hypertension, coronary artery disease and atrial fibrillation; diuretics are recommended in order to alleviate congestion symptoms. According to the ESC guidelines, management recommendations for patients with HFmrEF are the same as to patients with HFpEF (Ponikowski et al. 2016, Yancy et al. 2006). The ACC/AHA focused update of the guidelines in 2017 has included a class IIb recommendation for the use of aldosterone receptor antagonist in patients with stage C heart failure and LVEF ≥45%, elevated B-type natriuretic peptide (BNP) levels or HF admission within 1 year, eGFR >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L (Yancy et al. 2017).

A series of studies in different CV cell types demonstrated that mineralocorticoid receptor (MR) ablation improves cardiac remodeling in experimental models of heart failure providing evidence that aldosterone directly mediates cardiac hypertrophy, fibrosis and inflammation via MR in the CV system (Fraccarollo et al. 2011, Lother and Hein 2016). In particular, MR in vascular cells appears to be crucially involved in the translation of CV risk factors such as obesity, diabetes mellitus or age into cardiac disease. Following the hypothesis that those risk factors are closely associated with vascular inflammation as a key driver for diastolic dysfunction, these findings suggest a potentially beneficial role for MR antagonists in HFpEF.

Spironolactone has been shown to reduce myocardial fibrosis/cardiac extracellular matrix and to improve arterial stiffness in animal models (Lacolley et al. 2001). In line with the data from pre-clinical studies, a meta-analysis of 11 randomized trials showed that administration of an MR antagonist (MRA) was associated with an improvement in diastolic function assessed by echocardiography, as well as with a reduction in the concentration of circulating cardiac biomarkers reflecting the collagen turnover associated with myocardial fibrosis (Pandey et al. 2015).

Since activation of the MR by aldosterone is known to promote arterial hypertension, endothelial dysfunction, left ventricular hypertrophy, and progressive vascular, renal, and myocardial fibrosis, all of which may contribute to the development of HFpEF, the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial sought to test the value of spironolactone as a treatment for HFpEF (Desai et al. 2011).

In this randomized, double-blind trial, 3445 patients with symptomatic heart failure and a left ventricular ejection fraction of 45% or more were assigned to receive either spironolactone (15 to 45 mg daily) or placebo. The randomization was stratified according to whether the patient met the criterion for previous HHF within the last 12 months or natriuretic peptide (NP) elevation within 60 days prior to randomization.

Treatment with spironolactone did not significantly reduce the primary composite endpoint which was death from CV causes, aborted cardiac arrest, or HHF (Pitt et al. 2014b).

However, there was a beneficial effect of spironolactone observed in the stratum of patients enrolled on the basis of elevated baseline B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. Furthermore, post hoc analysis revealed marked regional differences in incidence rates, baseline clinical profiles, adverse events, and compliance with study therapies. A ≈4-fold lower incidence rate in the composite endpoint was identified between the 1678 patients randomized from Russia and Republic of Georgia compared with the 1767 enrolled from the United States, Canada, Brazil, and Argentina (the Americas). Also, the proportion of patients enrolled on the basis of elevated natriuretic peptide levels versus previous hospitalization for HF was higher in the Americas than in patients from Russia and Georgia. In the Americas region, spironolactone reduced the incidence of the

primary endpoint compared to placebo. In addition, treatment with spironolactone in patients being enrolled from the Americas was associated with more frequent hyperkalemia, elevations in creatinine, reductions in blood pressure, and less hypokalemia (Pfeffer et al. 2015).

Analysis of the TOPCAT results in the Americas led to the class IIb recommendation added in 2017 to the ACC/AHA guidelines (Yancy et al. 2017) and gives reason to hope that targeting the MR could result in improved clinical outcome in patients with HFpEF. TOPCAT also prompted further investigation in 2 additional global Phase 3 randomized, open label clinical trials (ClinicalTrials.gov NCT02901184; EudraCT #2017-000697-11) with planned total enrollment of 4500 participants evaluating spironolactone in HFpEF.

Molecular pharmacological considerations suggest that the balance between the interstitial, anti-remodeling effects, and the renal epithelial, natriuretic, and antikaliuretic effects of MR blockade can be modulated by the molecular structure of the pharmacological agent (Kolkhof and Borden 2012). There are 3 currently marketed MRAs, spironolactone, canrenone, and eplerenone with a steroidal chemical structure, similar to the natural ligands of the MR, aldosterone, and cortisol. In addition, the non-steroidal MRA esaxerenone has been approved in Japan. The similar structural and physicochemical properties of the steroidal MRAs determine the resulting pharmacological action, not only by their mode of binding to the MR, but also by their transport and distribution into different tissues and recruitment or blockade of tissue selective and ligand-specific co-factors (Kolkhof and Borden 2012).

Finerenone (BAY 94-8862) is an oral, selective and potent non-steroidal MRA of human MR in functional cellular transactivation assays combining *in vitro* spironolactone's potency with eplerenone's selectivity (Kolkhof and Borden 2012).

In animal models, finerenone reduced cardiac and renal hypertrophy, plasma prohormone of BNP and proteinuria more efficiently than in those treated with the steroidal MRA eplerenone, when comparing equi-natriuretic doses. Finerenone's tissue distribution pattern in rats was found to differ from the steroidal MRAs, i.e. spironolactone and eplerenone, which showed a higher accumulation of the drug equivalent concentration in kidney than in heart tissue, in contrast to finerenone which was found to be equally distributed in both the kidney and heart tissue (Kolkhof et al. 2014). The steroidal MRA spironolactone is known to interfere with the steroid hormone receptor, which can cause sexual side effects such as gynecomastia in men. However, finerenone is a non-steroidal and selective MRA *in vitro*, without any detectable affinity for the related androgen receptor; sexual side effects are therefore not expected to occur with finerenone at therapeutic dose levels.

In the safety and tolerability Phase 2 ARTS study (Pitt et al. 2013) finerenone in daily doses ranging from 2.5 to 10 mg was tested in comparison to placebo and spironolactone (25-50 mg) in patients with HFrEF and mild to moderate kidney disfunction. Results showed trends towards greater reduction in NT-proBNP levels with finerenone 10 mg compared with spironolactone, whereas increases in serum potassium were statistically significantly lower in finerenone arms compared to spironolactone. Moreover eGFR decline was smaller and incidence of worsening renal function was lower in all finerenone arms compared to spironolactone. Adverse events were reported in 79.4% of patients in the spironolactone arm and 53.1% in the highest dose finerenone arm which was comparable with the placebo group rates (50.8%).

In the dose finding Phase 2b ARTS-HF study in patients with worsening HFrEF and T2D and/or chronic kidney disease (CKD) (Filippatos et al. 2016) finerenone showed a decrease in NT-proBNP >30% in similar proportion of patients to that of eplerenone. However,

finerenone starting at the dose of 5-15 mg OD was observed to reduce CV hospitalization and death from any cause to a greater extent compared to eplerenone, whereas the finerenone dose of 10-20 mg was associated with the lowest rates of the composite clinical endpoint. Rates of hyperkalaemia defined as potassium ≥5.6 mmol/L any time post baseline in the finerenone dose of 10-20 mg (3.6%) were comparable to those in the eplerenone arm (4.7%).

Details of the results of the clinical and non-clinical development studies conducted with finerenone can be found in the Investigator Brochure.

2.1 Study Rationale

Study 20103 will be the first large-scale, long-term outcome study investigating the efficacy and safety of the non-steroidal MRA finerenone on morbidity and mortality in participants with heart failure (NYHA II-IV) and LVEF ≥40%, in comparison to placebo and in addition to standard-of-care therapy for congestion and comorbidities. As there is currently no approved therapy for heart failure with mid-range on preserved ejection fraction, placebo treatment was selected as comparator for this trial. Secondary endpoints will include time to total HF events; improvement in NYHA class from baseline to Month 12; change from baseline to Month 6, 9 and 12 in TSS of the KCCQ; time to first occurrence of composite renal endpoint: sustained decrease in estimated glomerular filtration rate (eGFR) ≥50% relative to baseline over at least 4 weeks, or sustained eGFR decline to <15 ml/min/1.73m^2 or initiation of dialysis or renal transplantation; time to all-cause mortality; and the safety and tolerability of finerenone.

An inappropriate release of aldosterone contributes to target organ damage found in heart failure, myocardial infarction, chronic renal failure, and hypertension. The extensive expression of the MR in the CV and renal systems, including the heart, endothelial cells, vascular smooth muscle cells, and kidney mesangial cells, provides further evidence for the role of aldosterone in CV and renal injury.

Blockade of the action of aldosterone and potentially other MR ligands such as cortisol has been demonstrated to be of benefit in HF. Results from a short-term Phase 2b study (ARTS-HF Study 14564) suggest that treatment with finerenone in addition to standard therapy for HF improves mortality and CV morbidity outcomes; however, long-term conclusive outcome studies examining whether non-steroidal MRAs can prevent CV events are still lacking. Study 20103 will be the first study to address these questions in this population.

Finerenone also has the potential to address the unmet medical need in patients with type 2 diabetes (T2D) and clinical diagnosis of CKD. The Phase 3 program with finerenone in patients with T2D and clinical diagnosis of CKD encompasses 2 placebo-controlled, large-scale, long-term outcome trials: Study 16244 examines whether finerenone can slow the progression of kidney disease and Study 17530 which is examining the effects of finerenone on CV outcomes. Both Phase 3 studies have enrolled over 13,000 participants since 2015 and are ongoing at the time of writing this protocol.

2.2 Background

Patients with HF exhibit an over activation of the renin-angiotensin-aldosterone system (RAAS) and the inappropriate release of aldosterone contributes to target organ damage, myocardial infarction, chronic renal failure, and hypertension. The extensive expression of the MR in the CV and renal systems, including myocytes, endothelial cells, vascular smooth muscle cells, and kidney mesangial cells, provides further evidence for the role of aldosterone in CV and renal injury.

Blockade of the action of aldosterone and potentially other MR ligands such as cortisol has been demonstrated to be of benefit in HF. Finerenone is a highly selective and potent non-steroidal mineralocorticoid receptor antagonist in development for treatment of chronic kidney disease in T2D patients as well as in HF.

A detailed description of the chemistry, pharmacology, efficacy, and safety of finerenone is provided in the Investigator's Brochure.

2.3 Benefit/Risk Assessment

In this study participants with heart failure (NYHA class II-IV) after recent HF decompensation and/or with elevated natriuretic peptides (BNP or NT-proBNP), will be given oral doses of finerenone once daily 10, 20 and 40 mg, depending on baseline eGFR, or placebo, in addition to standard-of-care therapies for congestion and comorbidities (i.e. RAAS inhibitors, beta-blockers, diuretics).

The eligibility criteria for this study 20103 have been chosen to adequately define a study population at high risk for worsening heart failure events, while excluding participants who may potentially be exposed to particular risks after study intervention administration or might benefit for intervention not included in the trial (i.e. amyloidosis, planned heart surgery).

Due to finerenone's mode of action, hyperkalemia is an important identified risk. However, in ARTS-HF (study 14564) the incidence of hyperkalemia was comparable between finerenone and eplerenone; and in ARTS (study 14563), all doses of finerenone resulted in significantly smaller serum potassium increase compared with spironolactone.

Worsening of renal function has been shown to occur with the steroidal MRAs, i.e. spironolactone and eplerenone (Rossignol et al. 2012). However, acute reductions in eGFR within the first 3 months upon starting RAAS blocking agents i.e. angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) or MRAs, in patients with CHF and/or CKD (Bakris and Weir 2000, Holtkamp et al. 2011) are postulated to reflect a hemodynamic response leading to reduced intraglomerular pressure, rather than therapy-induced damage to functioning nephrons (i.e. worsening of renal function). These changes are typically reversible on treatment withdrawal, and are associated with an attenuation of the long-term decline in eGFR (Heerspink et al. 2011).

In ARTS-HF (study 14564), the incidence of a relative decrease in eGFR of ≥30% from baseline was comparable between most of the finerenone dose groups (finerenone 2.5-5 mg n=8/119 (6.7%), finerenone 5-10 mg n=9/118 (7.6%), 7.5-15 mg n= 6/119 (5%), finerenone 10-20 mg n=7/130 (5.4%) and finerenone 15-20 mg n=15/120 (12.5%) except 15-20 mg OD) and the eplerenone (n=13/143 (9.1%) group (Filippatos et al. 2016) in supplementary material Table 10. In ARTS (study 14563), all doses of finerenone resulted in smaller eGFR decreases compared with spironolactone.

Potassium level and renal function will be closely monitored during treatment in this study (20103). In addition, patients will be included in this study only if serum/plasma potassium is ≤5.0 mmol/L. To minimize safety risks to the patient, starting doses of study medication will be chosen according to baseline renal function, and subsequent dose up-titration will be performed on the basis of measured potassium and eGFR values. Stopping rules for temporary and permanent discontinuation or dose reduction of study intervention based on potassium values will minimize the risk of hyperkalemia. At any time during the study, the investigator has the option to also down-titrate the study intervention, depending on serum potassium.

The high risk for CV mortality and morbidity in the population of this study (20103), taken together with the improved clinical outcomes seen with finerenone 10-20 mg OD compared with eplerenone in ARTS-HF (study 14564), indicate a positive risk-benefit assessment supporting the participation of participants in this study.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of finerenone may be found in the current Investigator's Brochure.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To demonstrate the superiority of finerenone to placebo in reducing the rate of the composite CV endpoint.	Composite primary endpoint: • Cardiovascular (CV) death and total (first and recurrent) HF events (HHF or urgent HF visit) in HF patients (New York Heart Association [NYHA] class II–IV) and LVEF ≥40%.
Secondary	
To determine superiority of finerenone to placebo for each secondary endpoint To assess the safety and tolerability of finerenone	Secondary endpoints: • Time to total (first and recurrent) HF events • Improvement in NYHA class from Baseline to Month 12 • Change from baseline to Month 6, 9 and 12 in Total Symptom Score (TSS) of the KCCQ • Time to first occurrence of composite renal endpoint: sustained decrease in estimated glomerular filtration rate (eGFR) ≥50% relative to baseline over at least 4 weeks, or sustained eGFR decline to <15 ml/min/1.73m^2 or initiation of dialysis or renal transplantation. • Time to all-cause mortality
Exploratory	
	Exploratory endpoints: • Time to first CV hospitalization • Time to first all-cause hospitalization • Total number of CV hospitalizations • Total number of all-cause hospitalizations • Time to first occurrence of the following composite endpoint: CV death or non-fatal CV event (i.e. non-fatal myocardial infarction, non-fatal stroke, or HHF) • Time to first occurrence of the following composite endpoint: sustained decrease in eGFR ≥57% relative to baseline over at least 4 weeks, or sustained eGFR decline <15 ml/min/1.73m^2 or initiation of dialysis or renal transplantation • Change in eGFR from baseline • Mean rate of change in eGFR as measured by total eGFR slope and its subcomponents acute and chronic slope • Change in UACR from baseline • Days alive and out of hospital • Time to new onset of atrial fibrillation • Change in health-related quality of life summary scores from baseline measured by the KCCQ and EQ-5D-5L

An **urgent HF visit** is defined as an urgent, unscheduled presentation with signs and/or symptoms of an acute HF decompensation requiring prompt medical attention and intensification of the existing HF treatment or initiation of a new HF treatment (Hicks et al. 2018). Further details and definitions will be provided in the Outcome/Endpoint Manual and Clinical Event Committee (CEC) Charter.

According to the addendum to International Council on Harmonisation (ICH) E9 (ICH_E9 (R1) 2019), the 5 attributes of the primary estimand are as follows:

a) Population:
As described by inclusion/exclusion criteria given in Section 5

b) Variable:
Number of unfavorable events including CV death and total (first and recurrent) HHF

c) Treatment condition:
Finerenone vs. placebo

d) Intercurrent events:
There are 3 important intercurrent events to consider: treatment discontinuation, CV death and non-CV death. For treatment discontinuation, a treatment policy strategy will be applied, i.e. patients will be followed up for events after discontinuing treatment and events and follow-up time after discontinuation of treatment will be included in the analysis. CV death will be counted as both an outcome event as well as a censoring event, so that a combination of a composite and a while-alive strategy is used. Non-CV death is assumed to be a censoring event, since the treatment is not assumed to have an effect on these events and interest lies in the treatment effect on composite events while patients are alive

e) Population-level summary:
Ratio of exposure-weighted composite event rates between finerenone and placebo. Exposure-weighted refers to patients being weighted according to their follow-up time in determining the rate.

4. Study Design

4.1 Overall Design

Study 20103 is a randomized, double-blind, parallel-group, placebo-controlled, multicenter, event-driven Phase 3 study with independently adjudicated clinical outcome assessments. The overall study design is displayed as the schema in Section 1.2.

This study will be conducted in patients with HF and LVEF ≥40%.

Participants will be randomized in a 1:1 ratio to either finerenone or placebo. The study is designed to be able to show an effect on the primary endpoint with a power of 90% at an alpha level of 5%. It is anticipated that 5500 participants will be randomized and approximately 6900 will be screened (screening failure rate of approximately 20%). A total of approximately 2375 total (first and recurrent) primary composite events are targeted.

The anticipated duration of the study will be approximately 42 months, with a recruitment period of 24 months. However, as an event-driven study, the actual length of the study will depend on the observed event rates, the participant recruitment rate, and the length of the recruitment period.

Enrolment in the trial may be capped based on the proportion of patients in certain LVEF categories, in each NYHA class, with/without atrial fibrillation, and by geographic region, among other variables, to ensure recruitment of a representative study population.

The randomization will be stratified by country/region and LVEF (<60%, ≥60%). Additional details will be described in the Statistical Analysis Plan (SAP).

Data from this study will be reviewed for efficacy and safety on an ongoing basis by an independent Data Monitoring Committee (DMC). A detailed plan for these assessments will be provided in the DMC Charter.

A CEC blinded to study treatment assignment will adjudicate all events that could potentially fulfill the criteria for the primary and some of the secondary endpoints during the study. The CEC Charter will describe the roles and responsibilities of the CEC and define the events to be adjudicated and the manner in which they will be adjudicated.

The SoA in Section 1.3 summarizes the schedule of procedures.

This study will be event-driven, and all randomized participants will remain in the study until either (1) an instruction is received from the sponsor after the targeted number of primary efficacy events has occurred, or (2) the study is terminated early at the recommendation of the DMC. Therefore, all participants, including those who have stopped taking study intervention, should be asked to attend all the protocol-specified study visits in order to perform all assessments as stipulated in the main SoA (Figure 1–1); for participants who permanently discontinued study intervention, minimal assessments (e.g. central lab for eGFR) will need to be performed as outlined in the Premature Discontinuation SoA (Figure 1–2). If a participant is unable to attend a study visit, every effort should be made to contact the participant by telephone or other means (by checking medical and public records) to determine if any endpoints were reached at the time the study visits were scheduled for the remaining duration of the study. All attempts to retrieve information about the participant should be documented in the participant's records.

Screening

After providing written informed consent, a Screening Visit to confirm the participant's eligibility will take place prior to randomization. The Screening Visit may take place on the same day as randomization (Visit 1). Local laboratories will be used to perform the eligibility assessments (potassium, creatinine/calculated eGFR). NT-proBNP or BNP levels will be evaluated as per medical records or collected locally to check eligibility. Please note the 2 distinct thresholds for NT-proBNP or BNP regarding eligibility (see inclusion criterion 6 in Section 5.1).

The higher threshold for NT-proBNP or BNP should be used for patients with prior history of atrial fibrillation or in case the cardiac rhythm is unknown. If a participant is hospitalized for HF, screening procedures and Visit 1 can take place while the participant is still in the hospital.

Treatment Period

Following a screening period of up to 2 weeks, eligible participants will be randomized in a 1:1 ratio to either finerenone or placebo. Participants with an eGFR ≤60 mL/min/1.73 m² measured at baseline will start with 10 mg OD (**dose level 1**) with a maximum maintenance dose of 20 mg OD (**dose level 2**), whereas participants with an eGFR >60 mL/min/1.73 m² measured at baseline will start with 20 mg OD (dose level 2) with a maximum maintenance dose of 40 mg OD (**dose level 3**).

There will be at least 2 scheduled visits within the first 3 months from randomization, Visit 2 will take place after 1 month and Visit 3 will take place 3 months after randomization; thereafter, scheduled visits will occur every 3 months until Visit 6 at Month 12. After 1 year from randomization, telephone contact visits will take place at Month 14 and from then *onwards* every 4 months (i.e. 18 months, 22 months onwards) *alternating* with on-site visits (i.e. 16 months, 20 months, onwards) until the end of the study is reached.

Up-titration is expected to occur after 4 weeks ± 7 days of treatment at Visit 2 (Month 1). Ideally, each participant will be on the maximum maintenance dose at this point. In the case of elevated potassium values, participants will be down-titrated to the next lower dose. Down-titrations can be performed at any time after the start of study intervention treatment, at any scheduled or unscheduled visit. At any scheduled or unscheduled visit, the dose of study intervention may be increased to the next possible higher dose, based on serum/plasma potassium level and provided the participant was already on a stable dose for 4 weeks ± 7 days.

Participants will attend an additional unscheduled safety visit 4 weeks ± 7 days after each up-titration; potassium levels and renal function will be monitored at this safety visit. In addition to the protocol-specified visits, participants may be seen at any time throughout the study at the discretion of the investigator.

If, in the opinion of the investigator, the participant cannot tolerate the maximum dose level of study intervention, the study intervention dose may be reduced to the next lower dose level. Provided the participant's safety is not affected, and if considered appropriate by the investigator, the participant should be re-up-titrated to the next higher dose level as soon as possible, preferably within 4 weeks, with the goal of keeping the participant on the maximum tolerated dose level for as long as possible. If the study intervention is temporarily interrupted, it should be re-introduced as soon as medically acceptable in the opinion of the investigator without compromising the participant's safety. See also Sections 6.1 and 7.1.1 for details.

Changes in the study intervention dose, including interruption/premature discontinuation or restart of study intervention, must be recorded in the electronic case report form (eCRF).

It is planned that all randomized participants will remain in the study until either:

a. an instruction is received from the sponsor after the targeted number of primary endpoint events have occurred

or

b. the study is terminated early at the recommendation of the independent DMC.

After randomization, study intervention discontinuation does not constitute the participant's withdrawal from the study, and all participants should continue to be followed up according to the Premature Discontinuation SoA (Figure 1–2).

All randomized participants, including any participant who experiences an event considered for the pre-specified primary or secondary endpoints, should continue to receive double-blinded treatment until the study is completed, provided there are no safety grounds for discontinuing treatment.

Post-treatment Follow-up Period

The period between a participant's last intake of study intervention and last visit in the study is referred to as the '*post-treatment follow-up period*'.

In the event of premature discontinuation of study intervention, participants are expected to continue to attend all protocol-specified study visits, and are expected to perform all scheduled assessments as described in the Premature Discontinuation SoA (Figure 1–2).

Any participant still taking study intervention at the point of end of study will enter the post-treatment follow-up period after stopping study intervention at the EOS Visit. For these participants, this phase will last 30 +5 days, and will end upon completion of the PT Visit (a telephone call visit; see Figure 1–1).

4.2 Scientific Rationale for Study Design

The inclusion and exclusion criteria allow the selection of an appropriate participant population and increase the likelihood of producing reliable and reproducible results, while guarding against exploitation of vulnerable persons. The proposed criteria are based on existing clinical knowledge and feedback from key opinion leaders involved in treatment of HF (NYHA II-IV).

4.3 Justification for Dose

Finerenone has been investigated with respect to safety, tolerability, pharmacodynamics and pharmacokinetics (PK) in 29 Phase 1 clinical pharmacology studies. PK were also investigated in all five Phase 2 studies for finerenone (CHF and CKD) with a total of 2017 patients.

The dose regimen of finerenone has been selected based on the results of the completed Phase 2b ARTS-HF and ARTS-DN studies.

The proposed doses for this Phase 3 study are as follows:

- For participants with an eGFR ≤60 mL/min/1.73 m^2 at baseline, the starting dose is 10 mg OD. From Visit 2 (Month 1) onwards and if potassium <5.0 mmol/l and eGFR decrease is <30%, the starting dose can be up-titrated to 20 mg OD

  and

- For participants with an eGFR >60 mL/min/1.73 m^2 at baseline, the starting dose is 20 mg OD. From Visit 2 (Month 1) onwards and if potassium is <5.0 mmol/l and eGFR decrease is <30%, the starting dose can be up-titrated to 40 mg OD.

Note: eGFR according to local laboratory values.

The following rationale for extrapolation to patients with LVEF ≥40% of this dose regimen is based on the expected safety profile of finerenone and the applicability of the exposure/response model founded on ARTS-HF data.

In the RALES study, the effect of spironolactone versus placebo on the outcome of patients with HFrEF was investigated and in the TOPCAT trial, HFpEF patients were treated either with spironolactone or placebo. In both studies, changes of serum potassium under spironolactone seem to occur in a similar time-dependent manner in HFpEF and HFrEF patients (Pfeffer et al. 2015).

In addition, the dose-response relationship is comparable in these two HF populations with potassium increases by 0.37 mmol/L after 3 months of treatment with spironolactone 25 mg in RALES and 0.3 mmol/L after 8 months of treatment with spironolactone in an average dose of 21.7 mg in TOPCAT.

Regarding effects on renal parameters, the dose-response relationship for spironolactone seen in the TOPCAT trial in HFpEF patients and the RALES trial in HFrEF patients was similar indicating that differences in LVEF are not expected to have clinically relevant influence on eGFR changes from baseline (serum creatinine change of 0.16 mg/dL after 8 months for average dose of 21.7 mg in TOPCAT and of 0.10 mg/dL after 3 months for 25 mg spironolactone in RALES).

Overall, the exposure/response relationship for both parameters in HFrEF patients is considered to be applicable for extrapolation to HFpEF patients under the assumption that baseline characteristics with regards to factors influencing PK such as body weight, and

baseline eGFR and baseline potassium levels are similar to that in the ARTS-HF study population. Under these conditions, the expected change of serum potassium is 0.1, 0.2 and 0.2 mmol/L and the expected relative eGFR change from baseline is 2.4, 3.1 and 3.8% for 10, 20 and 40 mg finerenone respectively in the total HF population. These ranges are expected to already represent the worst-case scenario since approximately 79% of the ARTS-HF populations are patients with eGFR ≤60 mL/min/1.73 m^2.

Rationale for finerenone 10 mg OD as minimal dose:

10 mg OD will be the minimal dose for the overall population. Up-titration will occur based on potassium and eGFR values and the investigator will have the option to down-titrate this finerenone dose based on its tolerability in terms of potassium values. This 2-step up-titration is consistent with current clinical practice to initiate treatment at a low dose, and to up-titrate the drug only if tolerated in order to avoid adverse effects on potassium and renal parameters.

In ARTS-HF, the 10-20 mg OD finerenone group compared to eplerenone showed a meaningful reduction in the exploratory composite endpoint comprising death from any cause, CV death, time to first CV hospitalizations and emergency presentation for worsening HF. Finerenone 10-20 mg OD showed a similar safety profile as to that of eplerenone with a lower incidence of treatment-emergent adverse events and similar rate of hyperkalemia (K^+ ≥5.6 mmol/L) (Filippatos et al. 2016).

In ARTS-DN, significant reductions in UACR at Day 90 compared to baseline were observed for 7.5 mg, 10 mg and 20 mg OD finerenone compared to placebo (Bakris et al. 2015). For the 10 and 20 mg doses, albuminuria had not returned to values similar to those at baseline 30 days after completion of treatment with finerenone suggesting a potential long-lasting effect of finerenone in structural changes in the kidney.

Rationale for finerenone 20 mg OD as maximal maintenance dose in patients with eGFR ≤60 mL/min/1.73 m^2:

A retrospective analysis of a national cohort (Einhorn et al. 2009) comprising 2,103,422 records from 245,808 veterans with at least 1 hospitalization and at least 1 inpatient or outpatient serum potassium record during the fiscal year 2005 showed that CKD and treatment with blockers of RAAS were the key predictors of hyperkalemia. The risk of hyperkalemia is increased with CKD, and its occurrence increases the odds of mortality within 1 day of the event.

Furthermore, patients with an age of 65 years or more with comorbid illness have the highest mortality when potassium levels rises above 5 mmol/L (Pitt et al. 2014a).

It was demonstrated in a subgroup analysis of the finerenone ARTS-HF study that potassium levels >6 mmol/L and eGFR decrease >40% were mainly found in the subgroup with eGFR ≤60 mL/min/1.73m^2 and UACR >300 mg/g (71% of the total population). Based on this data that showed an increase of finerenone concentrations in patients with impaired renal function associated with an increased risk of hyperkalaemia and eGFR reduction, it was decided to limit finerenone maximum dose among patients with eGFR <60 mL/min/1.73m^2.

Rationale for finerenone 40 mg OD as maximal maintenance dose in patients with eGFR > 60 mL/min/1.73 m^2:

NT-proBNP seems to be predictive for clinical outcome for both HFpEF and HFrEF patients. The prognosis of a patient depends on the NT-proBNP level and is similar in both HF populations (Kang et al. 2015). However, the responsiveness of this biomarker to MRAs seems to differ in patients with HFrEF and HFpEF. NT-proBNP was significantly reduced compared to baseline in the eplerenone arm of the EPHESUS study in HFrEF patients (Zannad et al. 2011) and in the ARTS-HF finerenone study (Filippatos et al. 2016). However, the initially observed difference to the placebo arm after 14 months vanished after 26 months in the RAAM-pEF study in HFpEF patients (Deswal et al. 2011). Spironolactone treatment was also found to decrease serum NT-proBNP levels in HFrEF patients (Ozkara et al. 2007), (Pitt et al. 2013). In the TOPCAT trial in HFpEF patients, however, hazard ratios for NT-proBNP terciles were reported to be all >1 indicating that spironolactone did not lead to a significant NT-proBNP change compared to placebo. Furthermore, a meta-analysis assessing MRA treatment in HFpEF patients showed that no reduction of BNP or NT-proBNP was observable in overall 5 studies (Chen et al. 2015). The only trial reporting significant changes in NT-proBNP in HFpEF patients was the ALDO-DHF study with a relatively stable HF population having only few comorbidities due to the study design (Edelmann et al. 2012).

Dose-response relationships for NT-proBNP for either spironolactone or eplerenone in HFpEF and HFrEF patients have not been reported so far, which makes it difficult to assess whether or not it is possible to bridge exposure/response models for NT-proBNP between these populations.

There are uncertainties associated with the responsiveness of NT-proBNP to MRAs. No *quantitative* prediction as to the changes of NT-proBNP for different finerenone doses were performed with an exposure/response model built on ARTS-HF data for finerenone in HFrEF patients. However, from a *qualitative* perspective, a linear exposure response from 2.5 mg up to 20 mg has been observed in the ARTS-HF trial indicating that NT-proBNP response was not saturated at 20 mg. This would suggest the possibility of greater effects on NT-proBNP at doses higher than 20 mg.

40 mg OD is the maximum maintenance dose of finerenone in patients with eGFR >60 mL/min/1.73 m^2. When the expected systemic finerenone exposure in these patients with mild renal impairment or normal renal function is compared with observed data in patients with moderate renal impairment receiving finerenone 20 mg in ARTS-HF, largely overlapping exposures are noted due to the effect of moderate renal impairment on area-under the curve (AUC; about 50% increase). These considerations on exposure in patients receiving 40 mg are complemented by exposure/response (PK/pharmacodynamics) analyses and simulations based on data from ARTS-HF. Changes in serum potassium and eGFR from baseline following administration of finerenone 40 mg to patients with normal renal function or mild renal impairment were also estimated to largely overlap with changes following administration of finerenone 20 mg to patients with moderate renal impairment. Generally, the drug effect on serum potassium and eGFR is estimated to be rather small even for 40 mg, compared to the impact of baseline values of the respective parameters. Based on model simulations, the expected change in steady-state serum potassium and eGFR following administration of finerenone 10, 20 and 40 mg OD to the HF population is an increase by 0.1, 0.2 and 0.2 mmol/L and a decrease by 2.4, 3.1 and 3.8%, respectively.

The safety of the 40 mg dose in patients with an eGFR >60 mL/min/1.73 m^2 will also be ensured by the starting dose of 20 mg with escalation to 40 mg only after measuring serum potassium and eGFR levels, and the possibility of down-titration.

Moreover, doses of 40 mg and higher have previously been found to be safe and well tolerated in the Phase 1 program in healthy volunteers, where 80 mg was the highest investigated single dose and 40 mg OD was the highest studied multiple dose regimen. Finerenone PK were linear across the investigated dose range.

In light of the aforementioned aspects, in particular with no reliable surrogate parameter and no additional information beyond the results from ARTS-HF and ARTS-DN to be expected, a specific dose-finding study in patients with HFpEF was not considered necessary.

Details of the results of the clinical and non-clinical development studies conducted with finerenone can be found in the Investigator Brochure.

4.4 End of Study Definition

The end of study treatment period will be announced when the targeted number of primary endpoint events has occurred, unless the study is terminated early because of a recommendation of the DMC.

After notification of study end, an EOS Visit should be scheduled as soon as possible (but within 4 weeks at the latest) for all participants still participating in the study, to determine whether the participant had an event for inclusion in the primary or secondary endpoints.

The date on which the final participant performed the EOS visit is defined as the primary completion date (see schema in Section 1.2).

Participants still on treatment will stop study intervention treatment at the EOS Visit and must perform the PT Visit 30 +5 days after their last dose of study intervention.

Participants no longer taking study intervention must also be contacted as soon as possible after issue of the notification of end of study and be asked to attend the EOS Visit.

For participants who have objected to releasing further information after withdrawing from the study, an updated vital status should be obtained by the investigator from publicly available data sources, wherever allowed by local regulations. The collection of vital status must be obtained within the timelines provided by the sponsor at this time.

The end of the trial as a whole is defined as the date of the last PT Visit of the last participant in the trial globally.

5. Study Population

Patients with a diagnosis of HF, NYHA class II–IV, and documented LVEF of ≥40%.

Prospective approval of protocol deviations to recruitment and enrollment 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 aged 40 years and older, at the time of signing the informed consent.

Type of Participant and Disease Characteristics:

2. Diagnosis of heart failure with NYHA class II–IV, ambulatory or hospitalized primarily for heart failure (if a hospitalized patient cannot be randomized as an in-patient, randomization as soon as possible after discharge is encouraged)
3. On diuretic treatment for at least 30 days prior to randomization
4. Documented LVEF of ≥40% measured by any modality within the last 12 months, at the latest at screening; if several values are available, the most recent one shall be reported. If LVEF was not measured in the past 12 months, a new measurement may be done at screening
5. Structural heart abnormalities based on any local imaging measurement within the last 12 months, latest at screening, defined by at least 1 of the following findings:
   - LAD ≥3.8cm, LAA ≥20cm^2, LAVI >30 mL/m^2, LVMI ≥115 g/m^2 (♂) / 95 g/m^2 (♀), septal thickness or posterior wall thickness ≥1.1 cm
6. NT-proBNP ≥300 pg/mL (BNP ≥100 pg/mL) in sinus rhythm and patient does not have an ongoing diagnosis of paroxysmal atrial fibrillation or NT-proBNP ≥900 pg/mL (BNP ≥300 pg/mL) in atrial fibrillation (or if atrial fibrillation status is unknown or if patient has an ongoing diagnosis of paroxysmal atrial fibrillation; see Section 4.1) for participants [1] obtained at the following time:
   - **Within 90 days prior to randomization** if patient had been **hospitalized for HF** requiring initiation or change in HF therapy or if patient had an **urgent visit for HF** requiring intravenous (IV) diuretic therapy, both within 90 days prior to randomization

   OR

   - **Within 30 days prior to randomization** if patient has **not** been hospitalized for HF nor had an urgent HF visit within the past 90 days.

[1] If a participant is being treated with Entresto (sacubitril/valsartan), the NT-proBNP value only (not BNP) should be used.

Sex

7. Male or female.

   Women of childbearing potential can only be included in the study if a pregnancy test is negative at screening and baseline and if they agree to use adequate contraception which is consistent with local regulations regarding the methods for contraception for those participating in clinical trials.

Informed Consent

8. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 Exclusion Criteria

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

Medical Conditions

1. eGFR <25 mL/min/1.73 m² at either screening or randomization visit.
   NOTE: one reassessment of eGFR is allowed at the screening and randomization visit, respectively
2. Serum/plasma potassium >5.0 mmol/L at either screening or randomization visit.
   NOTE: one reassessment of potassium is allowed at the screening and randomization visit, respectively
3. Acute inflammatory heart disease, e.g. acute myocarditis, within 90 days prior to randomization
4. Myocardial infarction or any event which could have reduced the ejection fraction within 90 days prior to randomization
5. Coronary artery bypass graft surgery in the 90 days prior to randomization
6. Percutaneous coronary intervention in the 30 days prior to randomization
7. Stroke or transient ischemic cerebral attack within 90 days prior to randomization
8. Probable alternative cause of participants' HF symptoms that in the opinion of the investigator primarily accounts for patient's dyspnea such as significant pulmonary disease, anemia or obesity. Specifically, patients with the below are excluded:
   - Severe pulmonary disease requiring home oxygen, or chronic oral steroid therapy
   - History of primary pulmonary arterial hypertension
   - Hemoglobin <10 g/dl*
   - Valvular heart disease considered by the investigator to be clinically significant
   - Body mass index (BMI) >50 kg/m^2 at screening
9. Systolic blood pressure (SBP) ≥160 mmHg if not on treatment with ≥3 blood pressure lowering medications or ≥180 mmHg irrespective of treatments on 2 consecutive measurements at least 2-minute apart, at screening or at randomization

10. Life-threatening or uncontrolled arrhythmias at screening and/or randomization including but not limited to sustained ventricular tachycardia and atrial fibrillation, or atrial flutter with resting ventricular rate >110 bpm
11. Symptomatic hypotension with mean systolic blood pressure <90 mmHg at screening or at randomization
12. Any primary cause of HF scheduled for surgery, e.g. valve disease such as severe aortic stenosis or severe mitral regurgitation by the time of screening or randomization
13. History of peripartum cardiomyopathy, chemotherapy induced cardiomyopathy, viral myocarditis, right heart failure in absence of left-sided structural disease, pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy including amyloidosis
14. Presence of left ventricular assist device by the time of screening or randomization
15. History of hyperkalemia or acute renal failure during MRA treatment for >7 consecutive days, leading to permanent discontinuation of the MRA treatment
16. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotrophin urine or serum test
17. Known hypersensitivity to the study intervention (active substance or excipients)
18. Hepatic insufficiency classified as Child-Pugh C at screening or randomization*
19. Addison's disease.

***** *Assessment of relevant laboratory parameters is only required if there is a clinical suspicion of anemia (as an alternative cause of HF symptoms) or hepatic insufficiency.*

Prior/Concomitant Therapy

20. Requirement of any IV vasodilating drug (e.g. nitrates, nitroprusside), any IV natriuretic peptide (e.g. nesiritide, carperitide), any IV positive inotropic agents, or mechanical support (intra-aortic balloon pump, endotracheal intubation, mechanical ventilation, or any ventricular assist device) within 24 hours prior to randomization
21. Participants who require treatment with **more than one** ACEI, ARB or angiotensin-receptor neprilysin inhibitor (ARNI), or **two simultaneously at randomization**
22. Continuous (at least 90 days) treatment with an MRA (e.g. spironolactone, eplerenone, canrenone, esaxerenone) within 12 months prior to screening. Last intake at least 30 days before randomization. Treatment with MRA should not be interrupted with the purpose of enrollment into the study
23. Concomitant treatment with any renin inhibitor or potassium-sparing diuretic that cannot be stopped prior to randomization and for the duration of the treatment period
24. Concomitant systemic therapy with potent cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors (e.g. itraconazole, ritonavir, indinavir, cobicistat, clarithromycin) or

moderate or potent CYP3A4 inducers, that cannot be discontinued 7 days prior to randomization and for the duration of the treatment period.

Other Exclusions

25. Any other condition or therapy, which would make the participant unsuitable for this study and will not allow participation for the full planned study period (e.g. active malignancy or other condition limiting life expectancy to less than 12 months)
26. Previous assignment to treatment during this study
27. Participation in another interventional clinical study (e.g. Phase 1 to 3 clinical studies) or treatment with another investigational medicinal product within 30 days prior to randomization
28. Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site)
29. Known current alcohol and/or illicit drug abuse that may interfere with the participant's safety and/or compliance at the discretion of the investigator
30. Participant is in custody by order of an authority or a court of law.

5.3 Lifestyle Considerations

No restrictions during the study are required other than those specified in 'Other Exclusions'.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly 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 (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (including reason), and eligibility criteria.

If a participant is not eligible during the Screening period for this study (20103), the participant may be rescreened once at a later time, provided the investigator believes that a change in the participant's condition makes him/her potentially eligible.

If a participant was eligible but could not be randomized due to exceptional logistical reasons (e.g. pandemic-related disruption), the participant may be re-screened once.

The following conditions are pre-requisites of re-screening:

1. Before re-screening, new written informed consent must be obtained
2. Allocation of a new participant number
3. All assessments for the study must be repeated
4. At least 3 months between initial screening and rescreening (except in the event of a participant being re-screened for exceptional logistical reasons).

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

The IxRS will determine the medication numbers for the study site investigator or designee to select for the participant.

Eligible participants will receive study intervention at the doses illustrated in Table 6–1, dispensed as outlined in the SoA (Section 1.3). The dose of finerenone will depend on the eGFR value at the Baseline Visit (determined by the local laboratory):

1. Participants with an eGFR ≤60 mL/min/1.73m² will start with 10 mg (dose level 1) and have a maintenance dose of 20 mg (dose level 2). Dose level 1 is the minimum dose and dose level 2 is the maximum permitted dose in this group of patients
2. Participants with an eGFR >60 mL/min/1.73m² will start with 20 mg (dose level 2) and have a maintenance dose of 40 mg (dose level 3). Dose level 1 is the minimum dose and dose level 3 is the maximum permitted dose in this group of patients.

The investigator is encouraged to up-titrate the dose of study intervention once the participant has been on a stable dose for 4 weeks (±7 days), either at the next regular visit or at an Up-titration Visit (see Table 6–1). Participants who do not tolerate their starting dose of 20 mg may be down-titrated at any point during the study, including between-scheduled visits if required for safety reasons. These participants may be up-titrated again based on the rules provided in Table 6–1. If the participant is already at the minimum dose, the study intervention can be interrupted at the investigator's discretion as detailed in Section 6.6, based on blood potassium levels and renal function which will be monitored throughout the study.

Intake of study intervention

Participants will be instructed to take one tablet of study intervention, preferably in the morning, at approximately the same time each day. The study intervention should be taken with a glass of water, with or without food.

Note: On the day of the first PK visit (Month 3) the participant should be instructed not to take the tablet at home in the morning but to have the PK sample collected first and then to take the study intervention at the study site.

Table 6–1 Dosage of Study Intervention for Administration

eGFR value at the Baseline Visit, based on local laboratory results:	**eGFR 25 to ≤60 mL/min/1.73m²**		**eGFR >60 mL/min/1.73m²**	
Participant randomized to group:	**Finerenone**	**Placebo**	**Finerenone**	**Placebo**
Starting dose:	10 mg finerenone OD (**Dose Level 1**)	Placebo OD	20 mg finerenone OD (**Dose Level 2**)	Placebo OD
Maintenance dose:	20 mg finerenone OD (**Dose Level 2**)	Placebo OD	40 mg finerenone OD (**Dose Level 3**)	Placebo OD
Minimum dose after down-titration:	10 mg finerenone OD	Placebo OD	10 mg finerenone OD	Placebo OD
Maximum dose after up-titration:	20 mg finerenone OD	Placebo OD	40 mg finerenone OD	Placebo OD
Study intervention intake	One tablet of study intervention OD, preferably in the morning at approximately the same time each day. Note: Study intervention will be administered at home, except on the day of the first PK visit when the tablet will be taken at the study site			
Missed intake	• If discovered within 16 hours after the scheduled time, the participant should take one tablet of study intervention as soon as possible • If discovered >16 hours after the scheduled time, this will be considered to be a 'missed' dose and the participant should wait and take the next tablet of study intervention at the usual (scheduled) time.			
Up-titration of dose • From Visit 2 (Month 1) onwards, at any scheduled or unscheduled visit • Follow guidance in Table 6–2 and Table 6–3 • Perform an additional safety visit 4 weeks ±7 days after each titration; monitor* potassium and renal function • Must be documented in the eCRF	Finerenone • Up-titrate study intervention to the next possible higher dose based on serum/plasma potassium level • eGFR decrease is <30% compared to last scheduled visit. Placebo • Sham-titrate.			
Down-titration of dose • At any scheduled or unscheduled visit • Follow guidance in Table 6–2 and Table 6–3 • Perform an unscheduled safety visit within an adequate timeframe proposed by the investigator for reason other than hyperkalaemia; monitor* potassium and renal function • Must be documented in the eCRF	• If potassium ≥5.5, down-titrate to the next lower dose level in a step-wise manner (dose level 2 to 1, or dose level 3 to 2) • If at dose level 1, interrupt study intervention treatment; study intervention should be re-introduced at dose level 1 as soon as the investigator considers it to be medically justified without compromising safety • If in the opinion of the investigator, the participant cannot tolerate the maximum dose level of study intervention, the study intervention dose may be reduced to the next lower dose level.			

Abbreviations: eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; OD = once daily, PK = pharmacokinetics

* NOTE: Potassium and eGFR according to local laboratory values

6.2 Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit if applicable, for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be kept in a secure environment and stored as per the instructions on the label.
3. The investigator or the head of the institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Investigator Site File.

6.3 Measures to Minimize Bias: Randomization and Blinding

Eligible participants will be centrally assigned to randomized study intervention at Visit 1 using an IxRS. The randomization will be stratified by country/region and LVEF (<60%, ≥60%). Additional details will be described in the SAP.

Treatment allocation will be done according to a computer-generated randomization list specified by the sponsor's responsible statistician and provided by the sponsor's randomization management group. Additional details are documented in the IxRS instruction manuals.

Study intervention will be dispensed at the study visits summarized in the SoA. Returned study intervention should not be re-dispensed to the participants.

Tablets containing 10 mg and 20 mg finerenone immediate-release (IR) tablets will differ in size from 40 mg finerenone IR tablets, but will be identical in appearance (size, shape, color) to matching placebo tablets. The packaging and labeling will be designed to maintain the blinding of the investigator's team and the participants. The study data will remain blinded until database lock and authorization of data release according to standard operating procedures.

In compliance with applicable regulations, in the event of a suspected unexpected serious adverse reaction (SUSAR) related to the blinded treatment, the participant's treatment code will usually be unblinded before reporting to the health authorities and ethics committees. For further details, see Section 8.3.6.

Bioanalytical staff will be unblinded according to the corresponding Bayer standard operating procedure (SOP). Pharmacometrics staff may also be unblinded according to Bayer SOPs.

Pharmacokinetic and exposure-response analyses will be performed using population approaches (popPK and popPK/PD, e.g. by non-linear mixed effect modeling). Analysis and report will be done under a separate cover. This evaluation might be started prior to database lock. If this is applicable, appropriate measures will be taken to maintain blinding of the study team, e.g. data will be stored separately, and members of the study team will neither have access to the randomization list nor to individual data.

The IxRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the responsibility for determining if unblinding of a participant's treatment

assignment is warranted. If the investigator is unavailable, and a treating physician not associated with the study requests emergency unblinding, the emergency unblinding requests are forwarded to the study specific emergency medical advice 24 hours/7 day service. The participant's safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

6.4 Study Intervention Compliance

To monitor compliance, the investigator will be required to complete a drug dispensing log for each participant. The date of dispensing the study intervention to the participant will be documented.

Overall compliance with study intervention intake should be between 80% and 120% of the scheduled dose at the end of study intervention treatment.

Study intervention will be dispensed according to the schedule provided in the SoA (Section 1.3). Participants will be instructed to bring all unused study intervention and empty packages at every (un)scheduled visit for accountability purposes. Any discrepancies between actual and expected amount of returned study medication must be discussed with the participant at the time of the visit, and any explanation must be documented in the source documents.

6.5 Prior and Concomitant Therapy

General considerations, Up until recently, there had been no treatment showing unequivocal mortality or morbidity benefit in participants with HFpEF and thus, pharmacologic treatments for HFpEF typically manage symptoms with diuretics being recommended in congested participants in order to alleviate symptoms and signs of HF. Recently, in a study in patients with HFpEF (Anker et al. 2021), SGLT2 inhibition with empagliflozin demonstrated a lower relative risk in the composite of cardiovascular death or hospitalization for heart failure, which was mainly related to a lower risk of hospitalization for heart failure with empagliflozin.

Arterial hypertension is highly prevalent among patients with HFpEF preceding the development of HF and contributing to CV morbidity and mortality by causing substantial CV structural and functional abnormalities by activating the RAAS.

To ensure that a relevant contributor to the development of HF and its outcome is well controlled, participants with uncontrolled blood pressure will be excluded; the treatment of comorbidities in particular arterial hypertension will be at the discretion of the investigator.

All concomitant medication until a participant's last visit will be recorded in the eCRF.

Concomitant therapies **not permitted during treatment with study intervention** are:

- Eplerenone, spironolactone, canrenone, esaxerenone, any renin inhibitor, or potassium-sparing diuretic
- **More than one** of the following: ACEI, ARB, ARNI
- Potent CYP3A4 inhibitors, and potent or moderate CYP3A4 inducers.

Drug interactions to look out for

The following should be used with caution, at the discretion of the investigator on a case-by-case basis:

- Potassium supplementation
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Trimethoprim and trimethoprim / sulfamethoxazole
- Any other medication known to raise potassium levels and/or cause deterioration in renal function.

The investigator is expected to regularly assess the participant's potassium levels and/or renal parameters (e.g. eGFR, creatinine), especially for those receiving these medications. For further details, see the SoA (Section 1.3).

Potassium-lowering agents (e.g. sodium polystyrene sulfonate, calcium polystyrene sulfonate) are allowed to be started during treatment with study intervention following their labeled indication.

Any use of potassium supplementation and potassium-lowering agents must be documented in the eCRF.

A list of the most common CYP3A4 inhibitors and inducers will be provided.

Caution

Concomitant use of finerenone in combination with weak or moderate CYP3A4 inhibitors such as: amiodarone, aprepitant, bicalutamide, chloramphenicol, dasatinib, imatinib, lapatinib, mifepristone, nilotinib, norfloxacine, tacrolimus, or verapamil increases finerenone exposure. Additional serum potassium monitoring should be considered, and make finerenone treatment decisions as directed in Table 6–2. More examples of weak or moderate CYP3A4 inhibitors will be provided separately.

6.5.1 Rescue Medicine

Not applicable.

6.6 Dose Modification

As described in Sections 6.6.1 and 4.3, the dose of study intervention should be adjusted (up-or down-titration) on the basis of potassium and eGFR levels.

6.6.1 Monitoring of Blood Potassium and Dose Adjustment

Guidance for the adjustment of dose after start of study intervention intake based on serum/plasma potassium levels is provided in Table 6–2.

Table 6–2 Potassium Levels and Guidance for Dose Adjustment

Serum / plasma potassium (K^+ mmol/L)		Action to be taken
First sample:		
<5.0		Increase to the next higher dose level (or continue at maximum permitted dose level)
≥5.0 to <5.5		Continue the current dose level
≥5.5 to <6.0		Down-titrate to the next lower dose if possible; if patient is already on dose level 1, interrupt study intervention. K^+ should be re-checked within 72 h of initial K^+ result awareness; follow **option a**
≥6.0		Interrupt study intervention and K^+ should be re-checked within 72 h of initial K^+ result awareness; follow **option b**
Second and subsequent sample:		
Option a	**<5.5**	Continue current dose
	≥5.5	Down-titrate to the next lower dose if possible, or interrupt study intervention and recheck K+
Option b	**<5.5**	Restart at dose level 1
	≥5.5	Continue to withhold study intervention, further monitoring of K^+. Restart at dose level 1 **ONLY** if K^+ is <5.0 mmol/L

The following aspects have also to be taken into consideration:

1. If the participant is already on dose level 1 no further decrease is possible after interruption, the same dose level should be re-started once serum/plasma potassium falls below 5.5 mmol/L. Serum/plasma potassium is to be measured at a safety visit 4 weeks ± 7 days after re-starting treatment or dose adjustment.
2. If the participant is on dose level 1 of study intervention, but hyperkalemia recurs soon after a previous event of hyperkalemia leading to interruption of study intervention, and there is no explanation for the recurring hyperkalemia event other than intake of study intervention, premature and permanent discontinuation of study intervention is recommended.
3. In case of hyperkalemia, it is at the investigator's discretion to take measures, including treatment and monitoring in accordance with local practice standards, beyond those reflected in Table 6–2.

6.6.2 Monitoring of Renal Function and Dose Adjustment

The dose of study intervention can be adjusted at the discretion of the investigator to account for renal function following the recommendations displayed in the table below Table 6–3.

Table 6–3 Renal Function Evaluation During Study

eGFR (mL/min/1.73 m^2) at any time after randomization	**Action to be taken**
Decrease ≥25% and <40% from baseline	1. Check for potential reversible causes: a. Concomitant medications known to affect renal function (e.g. NSAIDs, antibiotics) b. Adverse event (e.g. urinary infection, urinary retention, dehydration) 2. Address potential reversible causes if considered clinically appropriate
Decrease ≥40% from baseline	1. Check for potential reversible causes and address, as above. 2. At the investigator's discretion, study drug can be down-titrated or interrupted as follows: • Further monitor eGFR/creatinine • If eGFR/creatinine has reached acceptable levels (to be determined for the individual participant), please re-start study intervention at the next lower dose level (or dose level 1 if the participant was already on this dose). 3. Re-test at central laboratory after 4 weeks to confirm eGFR decrease of ≥50% or ≥57%*

Abbreviations: eGFR = estimated glomerular filtration rate; NSAID = non-steroidal anti-inflammatory drug
* Decrease based on central laboratory data.

6.7 Intervention After the End of the Study

No intervention is planned following the end of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

After randomization, discontinuation of study intervention (for any reason) does not constitute the participants' withdrawal from the study (see also Section 7.2).

Study intervention must be prematurely and permanently discontinued if any of the following occurs:

- Pregnancy of the participant (see also Section 8.3.5)
- The investigator is of the opinion that continuation of treatment with study intervention is harmful to the participant's well-being
- The randomization code is broken by the investigator, or other responsible person, when knowledge of the participant's treatment is required
- Any investigational drug other than the study intervention is used.
- Treatment with an MRA (eplerenone, spironolactone, canrenone, esaxerenone) for a period of more than 2 weeks.

Study intervention *may* be prematurely and permanently discontinued if any of the following occurs:

- Any suspected drug-related AE or SAE
- If any exclusion criterion applies during treatment
- If a significant violation of the protocol occurs, as defined by the sponsor and the coordinating investigator.

Participants who prematurely and permanently discontinue study intervention are expected to continue in the post-treatment follow-up period and to attend all protocol-specified study visits, and should be encouraged to perform all scheduled assessments described in the SoA for premature discontinuations (Figure 1–2).

Under certain circumstances, should the reason for permanent discontinuation of study intervention change, making it no longer applicable and the investigator is of the opinion it is in the subject's best interest to restart treatment, study intervention may be restarted on a case-by-case basis following comprehensive review by the Study Medical Expert.

If a participant no longer on study intervention is unable to attend the clinic for a study visit, a telephone consultation may be performed to determine if relevant health events /endpoints (e.g. development of CV or renal complications) have occurred. Ideally, a face-to-face visit should be performed at least once a year. The End of Study (EOS) visit is expected to be an onsite visit and should not be replaced by a telephone consultation unless an onsite visit is not feasible. Expected frequency of telephone contacts should be in line with the standard visit schedule, and therefore performed every 4 months. Ad hoc additional telephone contacts may also be requested (e.g. prior to the interim analysis) and made to the participant themselves or to other contact as provided by the patient, e.g. next of kin, primary physician (or local equivalent).

Note that study intervention may be temporarily discontinued (i.e. interrupted), as described in Section 6.6.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary Discontinuation

Resumption of study intervention after temporary interruption

Upon temporary interruption of the study intervention due to hyperkalemia, eGFR decrease, (S)AE, outcome events (OE), intolerability or any other reason, intake should be resumed as soon as medically acceptable at the discretion of the investigator. There is no defined maximum time limit for temporary interruption. In all cases, the reason for study intervention interruption must be recorded in the eCRF and the participant's medical records.

If the study intervention is interrupted for more than 7 days, the re-start should be performed at the next lower dose and the investigator should schedule an up-titration visit after 4 weeks (± 7 days) in order to monitor potassium levels and renal function (see Table 6–1). If a regular visit will be scheduled to take place 4 weeks ± 7 days after up-titration or re-start, the monitoring of potassium and renal function is assured and no up-titration visit has to be performed in addition. A restart and/or safety check visit is expected only if the investigator is aware of a temporary interruption that was initiated by the study participant.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, a premature discontinuation visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of study discontinuation and check for any further evaluations that need to be completed.
- The participant may be prematurely and permanently discontinued from the study intervention at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

General Procedure for Discontinuation/Withdrawal

In all cases, the reason for withdrawal of study intervention and/or of study participation must be recorded in the eCRF and in the participant's medical records.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she 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 clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, every effort should be made to contact him/her or a knowledgeable informant (e.g. family doctor, close relative, as indicated in the participant's medical records) by telephone to ask if any of the primary, secondary, or other endpoints have been reached at the scheduled visits for the remaining duration of the study. Attempts to contact the participant should be documented in the participant's records. If any participant refuses to be contacted by telephone (e.g. withdrawal of consent), every effort should be made to obtain vital status (alive or dead) information through consultation of public databases, wherever allowed by local regulation.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor 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, 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 participant enrollment/identification log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g. blood tests) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- All procedures and assessments should be conducted on the day of the visit (see Section 1.3).

8.1 Efficacy Assessments

All efficacy evaluations will be conducted according to the schedule detailed in the SoA.

The KCCQ and EQ-5D-5L are available in a high number of validated translations. Participants should complete each questionnaire alone and prior to the commencement of the other study visit procedures. However, participants in whose language a validated translation of the KCCQ or EQ-5D-5L is not available will be exempt from completing the questionnaire.

As an exception, in the following limited circumstances, the questionnaires may be narrated by someone designated/approved on study, such as a nurse or investigator, and completed based on answers given by the participant

- if the participant is legally blind or has poor visual acuity (including due to forgotten eyeglasses),
- if the participant is illiterate

The reason(s) for any non-completion of the questionnaires are to be recorded.

8.1.1 Kansas City Cardiomyopathy Questionnaire (KCCQ) and Total Symptom Score (TSS)

The **KCCQ** is a patient-reported disease-specific health status measure intended for the assessment of HF patients' perspectives of how their disease impacts their lives (Green et al. 2000). Patients are asked to recall how their HF impacted their life over a 2-week recall period. Response options for the 23 items (questions) are on a 5- to 7-point Likert-type scale with varying response options depending on the question. It requires, on average, 4 to 6 minutes to complete.

The **TSS** domain of the KCCQ was selected as the secondary endpoint because it is a direct measure of the hypothesized improvement of clinical symptoms. HF symptoms are subjective in nature and are best reported by the patient. The frequency and burden of clinical symptoms of HF in daily life include fatigue (KCCQ items 5 and 6), shortness of breath (KCCQ items 7 and 8), paroxysmal nocturnal dyspnea orthopnea (KCCQ item 9) and patient peripheral edema/swelling (KCCQ items 3 and 4) and are summarized in the TSS.

In addition to the KCCQ TSS, the KCCQ also measures the impact of patients' HF or their treatment in distinct domains: symptoms (with subscores for frequency and burden), physical limitations, quality of life, social limitations, self-efficacy and symptom stability. All scores are transformed to a 0-100 scale, with higher scores indicating a better outcome. The domains of self-efficacy (a measure of patient knowledge of preventing HF exacerbations) and symptom stability (a measure of symptom change over the previous 2 weeks) will not be considered measures of treatment efficacy.

8.1.2 EuroQoL (EQ-5D-5L)

The EuroQol (EQ-5D-5L) is an instrument used to assess the current health status of patients. It consists of 5 domains and one visual analogue scale. This instrument assesses self-reported health-related quality of life across the domains of mobility, self-care, usual activity, pain/discomfort and anxiety/depression of participants with an overall assessment of health status with a visual analog scale.

8.1.3 Patient Global Impression of Severity (PGIS) and Change (PGIC)

The PGIS question asks the patient to assess the current severity of their HF symptoms due to HF compared to the start of the treatment; *"Please choose the response below that best describes the severity of your **heart failure symptoms** (for example, shortness of breath, tiredness and swelling) over the past **two weeks."*** with the following response options: *much better, better, a little better, the same, a little worse, worse* or *much worse*.

The PGIC question asks the patient to assess the degree of change in their HF symptoms compared to the start of the treatment; "*Please choose the response below that best describes the overall change in your **heart failure symptoms** (for example, shortness of breath, tiredness and swelling) since you started taking the study medication. My heart failure symptoms are*:" with the following response options: *no symptoms, mild, moderate, severe* or *very severe.*

The 2 PGI questions will be administered in a sub-population of approximately 1200 patients, recruited at selected sites, at baseline (PGIS only) and at Visit 4 (Month 6), Visit 5 (Month 9) and Visit 6 (Month 12). They will be used as an anchor to provide an estimate of clinically meaningful in the KCCQ TSS. Details of the analysis, to be described in a separate SAP, will be conducted on a blinded dataset and reported separately from the CSR.

8.1.4 Assessment of NYHA class

NYHA class will be assessed according to the classification below:

- Class I: No limitation of physical activity
- Class II: Slight limitation of physical activity in which ordinary physical activity leads to fatigue, palpitation, dyspnea, or pain from angina; the person is comfortable at rest
- Class III: Marked limitation of physical activity in which less-than-ordinary activity results in fatigue, palpitation, dyspnea, or anginal pain; the person is comfortable at rest

- Class IV: Inability to carry on any physical activity without discomfort but also symptoms of heart failure or the anginal syndrome even at rest, with increased discomfort if any physical activity is undertaken.

8.1.5 NT-proBNP and hs-TnT

NT-proBNP and hs-TnT measurements during the study (including baseline) will be assessed by the central laboratory at the timepoints outlined in the SoA (Section 1.3). NT-proBNP or BNP measurements for eligibility check will be retrieved from medical records or assessed locally at screening.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

Safety assessments will include AEs, physical examination findings (if performed), and vital signs including heart rate and blood pressure assessment. Safety laboratory tests will include blood chemistry, hematology and urinalysis.

8.2.1 BMI and Weight

Body weight (in indoor clothing without shoes) will be measured at screening and all on-site scheduled visits, as weight gain can be the first clinical sign for HF. Height in centimeters will be assessed at screening visit for calculation of BMI. Hip and waist circumference in centimeters will be measured at the screening visit only.

8.2.2 Vital Signs

Vital signs will be assessed at all on-site scheduled visits.

Blood pressure and pulse measurements will be assessed preferably with a completely automated device and should be preceded by at least 10 minutes of rest for the participant in a quiet setting without distractions (e.g. television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 2 pulse and 2 consecutive blood pressure measurements, at least 2 minutes apart in sitting position. All blood pressure measurements will be recorded on the eCRF.

8.2.3 Clinical Safety Laboratory Assessments

Section 10.2 lists the clinical laboratory tests to be performed and the SoA specifies the timing.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered

clinically significant by the investigator (e.g. related to SAE or AE or dose modification), then the results must be recorded in the eCRF.

Central Laboratory Assessment

The name and the address for the central laboratory service provider can be found in the documentation supplied by the vendor. Only centrally analyzed blood samples will be considered for statistical analysis, unless otherwise specified. Details of the collections, shipment of samples and reporting of results by the central laboratory will be provided to the investigators in the Laboratory Manual.

- Laboratory evaluations (hematology, HbA_{1c}, clinical chemistry, urinalysis parameters, biomarkers [NT-proBNP and hs-TnT]) are shown in Section 10.2.
- SoA (Section 1.3) for the timing and frequency.

Local Laboratory Assessment

Blood safety samples will be taken from the Screening Visit onwards for analysis at the local laboratory.

- The following clinical chemistry parameters must be measured and the values documented in the eCRF
  - Serum/plasma creatinine (eGFR will be calculated automatically in the eCRF using the CKD-EPI formula)
  - Serum/plasma potassium.

From visit 2 (Month 1) onwards, study participants may have their local laboratory assessments taken up to 3 days prior to the study visit.

Potassium values should be recorded using a single decimal point (e.g. 4.5 mmol/L or mEq/L). In the event of hyperkalemia, please see Table 6–2 for guidance.

Up-titration or down-titration of the study intervention will be based on local potassium results and must be documented in the eCRF. Down-titration of the study intervention should occur primarily for safety reasons but can also be done for exceptional logistical reasons (e.g. study intervention supply issue).

Additionally, at screening, BNP or NT-proBNP can be measured if not available from clinical medical records.

In women of childbearing potential, a pregnancy test will be performed locally, at screening and baseline. Further pregnancy tests should be performed in participants of childbearing potential as required by national/institutional regulations (e.g. at every visit). At any time during study participation, additional pregnancy testing should be performed upon suspicion of pregnancy. Both serological and urine tests are acceptable.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3.

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or health care professional not involved in the study).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. They remain responsible for following up SAEs, or AEs considered related to the study intervention or study procedures, or those that caused the participant to discontinue the study intervention or the study (see Section 7).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs/SAEs will be collected from the start randomization at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of randomization but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section, except those related to study procedure; the latter have to be recorded as (S)AEs after informed consent has been obtained.

A surgical procedure that was planned prior to randomization by any physician treating the participant should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

Disease-related events and/or disease-related outcome events that are specified in the Section 8.3.6 will not be subject to (S)AE documentation. Thus they will not be recorded as SAEs on the AE page and will not be sent to the sponsor's Pharmacovigilance department. Instead, these events will be recorded on the Outcome Event pages of the eCRF. Consequently, they will neither be unblinded, not reported to regulatory authorities, IECs, or investigators even though the event may meet the definition of an SAE, see Section 8.3.6. All other SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstances should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated safety-relevant SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor 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.

The sponsor 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. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female and, if indicated, female partners of male participants will be collected after the start of study intervention and until the end of the follow-up period.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following disease-related events (DREs) are common in participants with heart failure and can be serious/life threatening:

- Worsening of heart failure, requiring hospitalization or urgent heart failure visit
- Worsening of renal function defined as a sustained eGFR decrease of 50% or more, or 57% or more compared to baseline; sustained eGFR decline below 15 mL/min/1.73m²; initiation of dialysis for at least 30 days or renal transplantation.
- Myocardial infarction

- Stroke
- New onset of atrial fibrillation or atrial flutter

These events are typically associated with the disease under study, and will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. In addition, they will neither be unblinded, nor reported to regulatory authorities, IECs, or investigators (see also Section 8.3.4 for details). Instead, these events will be documented only on the Outcome Event/Heart Failure pages of the eCRF and will undergo adjudication by an independent, blinded Clinical Event Committee as outlined in the CEC Charter.

Adverse events leading to death will be documented on the adverse event eCRF page and DREs leading to death will be documented on the outcome event eCRF page. All deaths will undergo adjudication.

An independent, unblinded DMC will monitor all events during the study and these DREs will also be analyzed after end of study and documented in the clinical study report. Should unexpected safety issues be identified, specific amendments will be implemented.

8.4 Treatment of Overdose

Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

In this trial, an overdose is defined as any occasion when the participant has taken (accidentally or intentionally) any dose higher than the maximal target dose prescribed in the protocol.

Overdose following administration of study interventions should be treated as clinically indicated based on symptoms and signs. There is no specific reversal agent for finerenone and the Sponsor does not recommend specific treatment for an overdose.

Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent (see Section 10.3.1).

8.5 Pharmacokinetics

For the investigation of systemic exposure to finerenone and its relationship with treatment effects, the plasma concentrations of finerenone will be determined at different time points using a sparse sampling approach in all study participants. The plasma concentration versus time data collected on the visits as outlined in SoA (see Section 1.3) will be evaluated descriptively, separated by dose and visit. Plots will be prepared by dose and visit of all individual plasma concentrations vs. actual relative study times (time of sample collection after time of study intervention administration).

The PK data may also be evaluated using non-linear mixed effect modeling (NONMEM). that may include attempts to identify whether the PK of finerenone is influenced by covariates and to explore exposure-response relationships. This evaluation, if performed, will be described in a separate analysis plan and will be reported separately.

At Visit 3 (Month 3), a trough sample for the determination of finerenone plasma concentrations will be drawn before intake of study intervention. At this visit, study intervention will be administered at the study site by study personnel and the exact time of

study intervention intake on the day before the visit and on the day of the visit and the exact sampling time will be recorded in the eCRF. Ideally, the study personnel should contact the participant prior to Visit 3 to remind them not to take the study intervention as usual in the morning at home. In case the trough sample cannot be taken (e.g. study intervention was taken at home), this may be postponed to Visit 4 or 5.

At Visit 6 (Month 12) and following visits as outlined in SoA (see Section 1.3), one blood sample for the determination of finerenone plasma concentrations will be drawn during the visit 1.5-10 hours after study intervention intake at home. The participants should be advised to take their drug as usual in the morning at home and recall the time of drug intake or note the time of drug intake on the contact card. The exact time of study intervention intake and the exact sampling times will be recorded in the eCRF.

The PK bioanalysis will be performed under the responsibility of Bayer Pharmaceuticals Bioanalytics Laboratory, BAG-PH-RD-RED-PCD-DMPK-PKBA-BA, 42096 Wuppertal, Germany.

Details about the collection, processing, storage and shipment of samples will be provided separately (e.g. sample handling sheets or laboratory manual).

8.6 Pharmacodynamics

Analysis of the pharmacodynamics parameters (e.g. blood pressure, heart rate, laboratory values) will be described in detail in the SAP.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

The biomarkers NT-proBNP and hs-TnT will be determined at the time points indicated in SoA for central laboratory assessments (Section 1.3).

Sample handling and storage - details on the collection, processing, shipment and storage of samples will be provided in separate documents (e.g. sample handling sheets or lab manual). Samples may be stored for a maximum of 15 years (or according to local regulations) following the end of the study at a facility selected by the sponsor to enable further analyses.

Other biomarkers

In addition to the biomarkers described above, other exploratory biomarkers related to e.g. the mode of action or the safety of the study intervention and similar drugs may be investigated. The same applies to further biomarkers deemed relevant to CV diseases and associated health problems. These investigations may include e.g. diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers. Samples (one serum and one plasma) for these analyses will be collected according to the SoA.

The results of biomarker investigations may be reported separately (e.g. in a biomarker evaluation report).

8.9 Immunogenicity Assessments

Not applicable.

8.10 Medical Resource Utilization and Health Economics

Additional analysis will be undertaken to assess the impact of treatment on Healthcare resource utilization, this may include hospitalization (by cause, frequency and duration), urgent heart failure outpatient visits, other treatments, tests and procedures as appropriate.

9. Statistical Considerations

9.1 Statistical Hypotheses

The primary endpoint is the composite of CV death and total (first and recurrent) HF events (HHFs and urgent HF visits). The primary analysis of this endpoint will be performed in the full analysis set using the planned treatment group, in line with the intention-to-treat principle.

Participants without an event of the primary composite endpoint at the time of analysis will be censored at the date of their last contact or date of non-CV death.

The primary analysis of the primary composite endpoint will be based on a stratified Andersen-Gill model (Andersen 1982) including treatment group as fixed effect and including country/region and LVEF (<60%, ≥60%) as stratification factors. Robust standard errors (sandwich estimator) will be used to account for correlations of event times within a participant. As shown by (Lin et al. 2000), the Andersen-Gill model with robust standard errors can be interpreted as a proportional rates model. After the authors of that paper, the model is also referred to as the 'LWYY model'. Let θ be the ratio of rates in the finerenone versus placebo group. In order to evaluate whether finerenone is superior to placebo in reducing the rate of the composite event of CV death and total HF events the following null hypothesis will be tested using the model above (see Section 9.5 for details regarding the nominal significance level):

$$H_0: \theta = 1 \quad \text{versus} \quad H_1: \theta \neq 1,$$

where a θ <1 represents a treatment benefit of finerenone over placebo.

A point estimate of the rate ratio together with a 95% confidence interval will be presented alongside the point estimate and hazard ratio for the competing event of non-CV death, calculated using a stratified Cox proportional hazards model. Additionally, plots and summaries of the mean cumulative function for the primary endpoint (Ghosh and Lin 2000) and cumulative incidence function for the competing event of non-CV death (Aalen and Johansen 1978) will be presented by treatment group.

In terms of the addendum to ICH E9 (ICH_E9 (R1) 2019), there are 3 important intercurrent events to consider: Treatment discontinuation, CV death and non-CV death. For treatment discontinuation a treatment policy strategy will be applied, i.e. patients will be followed up for events after discontinuing treatment and these events and the follow-up time will be included in the analysis. CV death will be counted as both an outcome event as well as a censoring event, so that a combination of a composite and a while alive strategy is used. It is thus assumed that patients could have had further events for HF, if they had not died. This seems appropriate, as including into the model that no further HF events can occur after death, for example by censoring patients at the end of the study, would induce a bias in favor of a

treatment group with more early deaths. Non-CV death is assumed to be a censoring event, since the treatment is not assumed to have an effect on these events and interest lies in the treatment effect on composite events while patients are alive. The primary analysis method has been investigated with extensive simulation studies and it has been confirmed that it keeps the alpha level and has good operating characteristics across a range of plausible scenarios.

9.2 Sample Size Determination

This is an event-driven study. The study is planned to last 42 months in total with a recruitment period of 24 months and participants are to be randomized 1:1 to finerenone and placebo. The sample size determination is based on a simulation study assuming a joint frailty model in order to account for the correlation between HF events and CV death, and to model participant heterogeneity with respect to baseline intensities/hazards. That is, given the participant-specific gamma distributed frailties, we assume a homogeneous Poisson process for HF events and an exponential distribution for the time to CV death. Furthermore, the frailty term is assumed to be the same for HF events and CV death.

The placebo rate parameter of the Poisson process and the hazard rate of the exponential distribution were first chosen as 0.014 HHFs/month per participant and 0.004 CV deaths/month per participant, respectively. These values lead to an observed annualized placebo rate of first composite events of 9.0 (events/ 100 participant-years) and an observed annualized placebo rate of CV death of 3.5. These observed rates are similar to rates observed in the literature, i.e. an annualized rate of first composite event of 9.1 was observed in the CHARM-Preserved trial, 8.9 was observed in PARAGON-HF and 8.5 in the BNP stratum of the TOPCAT trial. Regarding CV death, an annualized placebo rate of 3.9 per 100 participant-years was observed in CHARM-Preserved, 3.1 was observed in PARAGON-HF and 3.9 was also observed in the TOPCAT BNP stratum. Since it is planned to recruit more participants with a very recent hospitalization than in previous trials, which would be at a higher risk of events, the rate parameters were subsequently increased by 25% for CV death leading to a rate of 0.005125 CV deaths/ month per participant. For HF events, the rate was increased by 30% to 0.0182 HF events /month per participant to also account for the inclusion of urgent HF visits, which have not been included in primary endpoint of the former trials. The additional increase in event rate is in line with the increase reported for PARAGON-HF (Solomon et al. 2019), Supplementary Appendix). The resulting observed annualized placebo rates are then 12.5 for first composite events and 4.6 for CV death. The frailty variance is chosen as 5.0, so that the ratio of total composite to first composite events is about 1.8. Similar ratios have been observed across a number of heart failure studies (Anker and McMurray 2012). Non-CV deaths are simulated as exponentially distributed censoring events with a rate of 0.0016 non-CV deaths/month per participant, leading to approximately 70% of all deaths being due to CV causes.

As treatment effects, a hazard ratio for CV death of 0.8 and a rate ratio for heart failure events of 0.75 are assumed. With approximately 5500 randomized participants, it is expected to observe approximately 1310 first events and approximately 2375 total events leading to a power of 90% to show an effect at a two-sided alpha level of 5%. Under these assumptions it is expected to observe a 19% decrease in the rate of the primary endpoint for finerenone. An annual drug discontinuation rate of 5% is assumed, with finerenone participants having the same risk of events as placebo participants after discontinuation and no change in event rate for discontinuing placebo participants. Participants discontinuing study intervention are expected to remain under observation in the study. Table 9–1 below shows the resulting

power under deviations from the assumed treatment effect as well as the power for a time-to-first composite event analysis. As it would be desirable for a single pivotal trial to obtain a higher level of evidence so that the power at an alpha level of 1% is also given.

Table 9–1 Power for Assumed Sample Size Scenario and Some Variations

Sample size	Rate ratio HF events	Hazard ratio CV death	Power primary α=5%	Power primary α=1%	Power Time-to-first α=5%
5500	0.75	0.80	90%	74%	74%
	0.75	0.90	89%	73%	64%
	0.78	0.90	79%	58%	53%
	0.72	0.80	95%	86%	82%

Abbreviations: α = alpha; CV = cardiovascular; HF = heart failure

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Table 9–2 Populations for Analyses

Population	Description
Enrolled	All participants who sign the informed consent form (ICF).
Randomly assigned to study intervention	All participants randomly assigned to study intervention.
Safety analysis set (SAF)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Full analysis set (FAS)	All randomized participants. Participants will be analyzed according to the intervention they were randomized to. Only potential reasons for exclusion would be a clearly erroneously randomization, or major GCP violations, for example, a serious suspicion of fraud.
Pharmacokinetic analysis set (PKS)	All finerenone-treated participants (with the exception of participants excluded on the grounds of critical GCP violations) with at least 1 valid finerenone plasma concentration and without validity findings which would interfere with the evaluation of the PK data.

Abbreviations: GCP = Good Clinical Practice; PK = pharmacokinetic

9.4 Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

Summaries and analyses to address the impact of COVID-19 will also be defined in the SAP.

9.4.1 Efficacy Analyses

9.4.1.1 Primary Efficacy Variable

The primary efficacy variable is the composite endpoint of CV death and/or total (first and recurrent) events for HF. See Section 9.1 for a description of the primary analysis.

As part of the primary analysis, a separate estimate of the treatment effect for CV death as one of the components of the primary endpoint will be obtained. The second component of total HF events will be a secondary endpoint and analyzed as described in section 9.4.1.2. The main cause-specific treatment effect estimate for CV death will be derived from a stratified Cox proportional hazards model for time to CV death and the main p-value from a stratified log-rank test. A cause-specific treatment effect estimate for the competing event of non-CV death will also be calculated using a stratified Cox proportional hazards model and presented with associated 95% confidence interval. The cumulative incidence functions for time to CV death and time to non-CV death will also be calculated using Aalen-Johansen estimates.

Note that the study is not powered to show an effect on CV death alone. While this is the case, a sufficient number of deaths are expected so that an excess risk in mortality can be excluded. Under the assumptions of the sample size determination, approximately 535 CV deaths and approximately 775 all-cause deaths are expected to occur in the study. Even though no formal statistical tests for exclusion of an increased risk will be performed, these expected event counts would result in a relatively high power to exclude hazard ratios on all-cause mortality (ACM) above 1.15 and 1.25. Table 9–3 provides the respective power values under different assumed values for the true hazard ratio on CV death and assuming no treatment effect on non-CV deaths (HR_{NonCVD}=1.0). Similar to the primary endpoint, a treatment policy strategy is used for treatment discontinuation. With exclusion of a certain hazard ratio value it is meant that the upper limit of a 95%-confidence interval is below the value.

Table 9–3 Power to Exclude Increased Hazard Ratio on All-Cause Mortality Under Different Assumed Treatment Effects on CV Death

True HR_{CVD}	Exclude HR_{ACM} >1.15	Exclude HR_{ACM} >1.25
0.8	94%	>99%
0.9	78%	97%
1.0	52%	88%

Abbreviations: ACM = all-cause mortality; CV = cardiovascular; CVD = cardiovascular death; HR = hazard ratio

As supportive analysis, a stratified Cox proportional hazard regression analysis of time to first composite event (CV death or first HF event) will also be performed and a plot of Aalen-Johansen estimates of the cumulative incidence function will be provided. An additional analysis of the primary endpoint will exclude urgent HF visits and consider only CV deaths and HHFs as events.

As a sensitivity analysis, the number of primary composite events will also be analyzed using a negative binomial regression model including stratification factors and treatment group as covariates and log follow-up time as an offset parameter.

A total-time approach considering times from randomization to the onset of first, second, third composite event using a (Prentice et al. 1981, Wei et al. 1981) model will be applied. This model enables analysis of the cumulative effect on the primary endpoint from randomization (i.e. the effect on second event includes the effect on the first, and the effect on third event

includes the effects on the first and second). The corresponding individual hazard ratios with 95% CIs comparing treatment groups on the first, second, and third event will be presented. In addition a conditional gap-time model according to Prentice et al will be applied to obtain hazard ratio estimates with 95% CIs for the time from first to second and from second to third event (note that this gives a non-randomized comparison). Both models will employ robust standard errors and include the stratification factors and treatment group as fixed effects.

Events that could potentially fulfill the criteria for primary efficacy variables during the study will be evaluated by the CEC. Definitions of individual endpoints (e.g. CV death) will be provided in the Endpoint Manual.

Additional supportive analyses will be considered and will be described in the SAP.

9.4.1.2 Secondary Efficacy Variables

Secondary efficacy variables are the following:

- Time to total (first and recurrent) HF events
- Improvement in NYHA class from Baseline to Month 12
- Change from baseline to Month 6, 9 and 12 in TSS of the KCCQ
- Time to first occurrence of composite renal endpoint:
  sustained decrease in eGFR ≥50% relative to baseline over at least 4 weeks, or
  sustained eGFR decline <15 ml/min/1.73m^2 or initiation of dialysis or renal transplantation.
- Time to all-cause mortality.

The secondary hypotheses will be formally tested, and statistical inferences will be made only if the primary hypothesis is rejected. The testing strategy of the secondary endpoints is as follows:

1. Total HF events will be tested at the same two-sided significance level as the primary endpoint (hereafter denoted α_p - see Section 9.5 for details regarding the nominal significance level)
2. Only if the hypothesis for the secondary endpoint total HF events is rejected, the NYHA class and KCCQ endpoints will be tested using the Bonferroni-Holm procedure, i.e. if at least one of the hypotheses of the two endpoints NYHA class and KCCQ can be rejected at the two-sided $\alpha_p/2$ significance level, the remaining of the two endpoints will be tested at the two-sided α_p significance level.
3. Only if the hypotheses for all previous secondary endpoints are rejected, the composite renal endpoint will be tested at the two-sided α_p significance level.

As a hard endpoint and objective indicator of benefit-risk, time to all-cause mortality will be tested at a full two-sided significance level of 5%, after the rejection of the primary hypothesis. The second component of the primary endpoints, CV death, will also be tested at the same significance level as the primary endpoint after the primary hypothesis is rejected. Testing of time-to-all-cause mortality and CV death will thus be done outside of the alpha-preserving procedure for the primary and other secondary efficacy variables (Total HF events, NYHA class, KCCQ, renal composite).

Time to total HF events will be analyzed with a joint frailty model (Rogers et al. 2016). This model gives a treatment effect on total HF events which is adjusted for a potential treatment effect on CV death. An effect on CV death might otherwise dilute the effect seen on the hospitalizations, i.e., an effective treatment will prevent CV deaths especially in the more severely ill participants, which then potentially realize many hospitalizations. The joint frailty model will be fitted using the method described in the paper by (Liu and Huang 2008) where the unknown baseline hazard for CV death and unknown baseline intensity for HF events are approximated by piecewise constant functions. A gamma frailty distribution will be assumed. As a sensitivity analysis a joint frailty model with constant hazard and intensity functions will be fitted as well. The flexible model can sometimes have convergence issues, should this occur, the estimate of HF events treatment effect of the model with the constant baseline functions will be considered to be the main estimate. The estimate from the joint frailty model for CV death will be considered supportive for the analysis of this component. The main analysis for the CV death component is described under the primary efficacy variable in section 9.4.1.1. As supportive analysis, a stratified Cox proportional hazard regression analysis of time to first HF event will also be performed.

The percentage of participants with improvement in NYHA class from Baseline to Month 12 will be analyzed with a logistic regression model including factors for treatment group and stratification levels. A patient is considered as having improved in NYHA class, if the NYHA class at Month 12 (Visit 6) is at least one category improved compared to the baseline visit. A composite strategy will be applied to those cases, where no measurement at Visit 6 is available, e.g. due to death or lost to follow-up. That means these patients are considered not improved in NYHA class. Odds ratio and two-sided 95% confidence intervals will be provided for the comparison of finerenone vs. placebo treatment group. In addition, change from baseline in NYHA class will be summarized descriptively using shift tables, presented by visit and any time post-baseline.

The absolute change from baseline including measurements up to Month 12 of the TSS of the KCCQ will be analyzed by a repeated measures mixed model including the factors treatment group, baseline, visit, baseline-by-visit interaction, and factors for the stratification levels. Differences between the finerenone and the placebo treatment groups will be calculated with two-sided 95% confidence intervals. The comparison assumes a common treatment effect across month 6, 9 and 12 and will be considered primary. This analysis will investigate the effect on the TSS of the KCCQ while patients are alive and irrespective of any permanent treatment discontinuation. This means that all observed values will be included in the analysis without any specific imputation. A supportive analysis will apply a worst-case imputation for death which means that if a patient dies, a worst score of 0 for the TSS will be imputed for all subsequent visits after the patient's death. Treatment effects at Month 6, 9 and 12 will also be investigated individually by adding a treatment-by-visit interaction into the model. The primary analysis of the secondary time-to first event variables (i.e., composite renal endpoint and ACM) will be done with a stratified log-rank test for testing and a stratified Cox proportional hazards model for obtaining a point estimate with 95% confidence interval. The Cox proportional hazards model will be stratified according to the stratification factors and include treatment group as fixed effect. For the composite renal endpoint, the cause-specific point estimate with 95% confidence interval for the competing event of death will also be presented. Cumulative incidence function plots and summaries (calculated using Aalen-Johansen estimates) will be produced for the composite renal endpoint and the competing event of death. In addition, components of the composite renal endpoint will be analyzed. Furthermore, Aalen-Johansen plots will be displayed for the ACM endpoint.

Only central laboratory measurements before initiation of dialysis or renal transplantation will be considered for the definition of the individual eGFR-based components of the renal endpoint. At the up-titration, restart and safety check visits, only a local laboratory measurement is obtained. These values will be checked for a potential eGFR event and, in case of decline, the investigators will be advised to retest eGFR centrally in an unscheduled visit; determination of an eGFR event will then be based on this value. Events will be counted from the day of randomization until the EoS visit. If an initial decrease in eGFR occurs on the EoS visit, there will be another confirmatory measurement taken at least 4 weeks later to confirm the initial decrease. The individual components "Sustained decrease of eGFR ≥50% from baseline over at least 4 weeks" as well as "Sustained eGFR decline <15 ml/min/1.73m^2" will be programmatically derived. Only in case the eGFR decrease was confirmed by at least one additional eGFR measurement taken at least 4 weeks later, it will be considered as a sustained decrease and counted for the renal endpoint. The date used for the analysis will be the date of the initial sample exceeding the threshold. In case there was no confirmatory assessment, events will only be counted for the renal endpoint when the patient died after the initial decrease or the patient went on renal replacement therapy such as dialysis or transplantation. If there is an intermediate measurement that does not confirm the initial decrease, the event will not be counted for the renal endpoint.

The other two components of the renal endpoint, i.e. initiation of dialysis or renal transplantation, will be adjudicated. To account for events of initiation of dialysis after the last eGFR is recorded at a clinic visit, such events will be included in the efficacy analysis of the composite renal endpoint if they occur in the period up to one day before the next planned clinic visit. Censoring will be applied at next protocol scheduled visit plus 1 month. For a death in this period, the date of death will be used as the censoring date. Randomized participants without an event of the composite renal endpoint at the time of analysis will be censored at the date of their last visit when complete information on all components of the composite renal endpoint is available, up to and including the EoS visit (should this visit satisfy this rule), or date of death using a time window next protocol scheduled visit plus 1 month as above if a subsequent clinic visit had been planned.

Additional supportive analyses will be considered and will be described in the SAP. The following subgroups will be considered in exploratory subgroup analyses for the primary and secondary efficacy variables. This will include descriptive statistics and a statistical test for interaction.

The randomization will be stratified by country/region and LVEF (<60%, ≥60%). The most important subgroups besides stratification factors are given below (with further details and subgroups provided in the SAP):

- Baseline serum potassium (≤4.5, >4.5 mmol/L)
- eGFR category at baseline (eGFR 25 to <45, 45 to <60, ≥60 mL/min/1.73 m²)
- Atrial fibrillation at baseline ECG (present, absent)
- Diabetes mellitus at baseline (present, absent)
- HHF (very recent [≤7 days before randomization], recent [>7 days – ≤3 months], >3 months - ≤6 months, >6 months - ≤9 months, >9 months - ≤12 months, no index).

It is anticipated that in these proposed subgroups for analysis, differences in treatment effects may be observed according to the screening or baseline characteristics defined, due in part to the differences in the risk of clinical events expected in the different subgroups.

Furthermore, subgroup analysis usually required will be performed, including the following subgroups:

- Race
- Sex
- Age group.

9.4.1.3 Exploratory Variables

- Time to first CV hospitalization
- Time to first all-cause hospitalization
- Total number of CV hospitalizations
- Total number of all-cause hospitalizations
- Time to first occurrence of the following composite endpoint: CV death or non-fatal CV event (i.e. non-fatal myocardial infarction, non-fatal stroke, or HHF)
- Time to first occurrence of the following composite endpoint: sustained decrease in eGFR ≥57% relative to baseline over at least 4 weeks, or sustained eGFR decline <15 ml/min/1.73m^2 or initiation of dialysis or renal transplantation
- Change in eGFR from baseline
- Mean rate of change in eGFR as measured by total eGFR slope and its subcomponents acute and chronic slope
- Change in UACR from baseline
- Days alive and out of hospital
- Time to new onset of atrial fibrillation
- Change in health-related quality of life summary scores from baseline measured by KCCQ and EQ-5D-5L

Exploratory time-to-event variables will be analyzed using the stratified log-rank test and the stratified Cox proportional hazards model.

The total number of CV hospitalizations will be analyzed using an LWYY model, similarly to the primary efficacy endpoint, and will be summarized descriptively by treatment group together with the annual rate of CV hospitalizations. These summaries and analyses will be repeated for all-cause hospitalizations.

The absolute change of eGFR to baseline at each visit until Visit 10 (Month 24) will be analyzed by a mixed model with the factors treatment group, baseline eGFR, visit, treatment-by-visit interaction, baseline-by-visit interaction, and factors for the stratification levels (region and LVEF). Differences between the finerenone and placebo groups at each visit will be calculated, and corresponding two-sided 95% confidence intervals will be computed. Change in UACR from baseline will be analyzed in an identical fashion.

Frequency tables will be generated for the number and percentage of patients with a relative decrease in eGFR of ≥25%, ≥30%, ≥40%, ≥50% and ≥57% from baseline. The analysis will be performed for each visit and for any time post-baseline.

The rate of change of eGFR will be compared between the finerenone and the placebo group by estimating the total eGFR slope using available assessments from baseline to planned end of the treatment period. It is assumed that changes in the mean response can be expressed in terms of a linear trend, and the treatment effect can be expressed in terms of the difference in slope between finerenone and placebo. For the analysis of the total slope, the serial change in eGFR will be modeled using a two-slope linear spline mixed-effects model in which a fixed change point will be defined to separate acute and chronic eGFR slope at month 3 (section 2.1 of (Vonesh et al. 2019)). In addition to fixed effects for the treatment, time (continuous) and treatment by time interaction, the model will include fixed effects for the stratification factors and random effects for the intercept, acute slope (baseline to month 3), and chronic slope (month 3 to planned end of treatment period). An unstructured covariance will be used to model the between-participant errors. Within-participant errors are assumed to be homogenous. Linear contrasts will be constructed to estimate the acute, chronic, and total slope in eGFR. LS means and differences of the acute, chronic and total eGFR slope for finerenone and placebo group will be provided with 95% confidence intervals (and corresponding p-values for the differences).

Days alive and out of hospital (DAOH) will be summarized descriptively by treatment group; the number and percentage of DAOH with respect to total potential follow-up time will be provided alongside the number and percentage of days dead and days in hospital, including breakdown into type of death and hospitalization, respectively. These analyses will be performed overall and separately by the stratification factors (region and LVEF).

DAOH will be analyzed by an ANCOVA model including potential follow-up time, treatment group, and stratification factors as fixed effects.

DAOH will be analyzed once considering the total potential follow-up time and once considering only the first year of follow-up.

For the KCCQ, 3 summary scores (symptom frequency score, total symptom score, and overall summary score) will be derived. For the KCCQ symptom frequency scores, the following will be presented by visit and treatment group: number of observations, number of missing values, minimum, first quartile, mean, standard deviation, median, third quartile, and maximum, including the changes from baseline.

For the EQ-5D-5L, summary scores will be calculated from the 5 dimensions according to the scoring instructions from Europe and the US (refer to the EQ-5D-5L User Guide (EuroQoL_Group 2013) and to the EQ-5D Value Sets (Szende et al. 2007). The values and the changes from baseline of the summary scores and the EuroQol Group visual analogue scale (EQ VAS) will be summarized by treatment group and visit using the same descriptive statistics as for the KCCQ.

9.4.2 Safety Analyses

All safety analyses will be performed on the SAF.

The following safety procedures and variables will be assessed during the study:

- SAEs and AEs leading to discontinuation of treatment with study intervention
- Change in body weight from baseline
- Change in serum potassium from baseline
- Number of participants with hyperkalemia (serum potassium ≥5.5 mmol/L)
- Number of participants with severe hyperkalemia (serum potassium ≥6.0 mmol/L)
- Number of participants with hospitalization for hyperkalemia
- Number of participants permanently discontinuing study intervention due to hyperkalemia
- Change in vital signs (heart rate, SBP and DBP) from baseline
- Change in renal function measured by eGFR (CKD-EPI formula) change from baseline
- Number of participants with hospitalization for worsening of renal function
- Number of participants permanently discontinuing study intervention due to worsening of renal function
- Changes in laboratory values from baseline.

An overall summary of all AEs and treatment emergent AEs (TEAEs) will be generated by treatment group.

The number and percentage of patients with TEAEs, post-treatment AEs occurring more than 3 days after last intake of study intervention, treatment-emergent SAEs, treatment-emergent study intervention-related AEs, treatment-emergent study intervention-related SAEs, TEAEs causing premature and permanent discontinuation of study intervention, treatment-emergent non-serious AEs, TEAEs by maximum intensity, drug-related TEAEs by maximum intensity will be summarized by treatment group using MedDRA terms grouped by Primary System Organ Class and Preferred Term.

The number of patients with treatment-emergent (until 3 days after last study intervention administration) abnormal laboratory values above or below the normal range will be tabulated by the laboratory parameter and treatment group.

Summary statistics including changes from baseline will be calculated by treatment group and visit for all quantitative laboratory parameters, i.e. for hematology, clinical chemistry and urinalysis. Geometric statistics and ratios to baseline will be presented for urinary albumin-to-creatinine ratio (UACR), creatinine, and NT-proBNP, instead of arithmetic statistics with changes from baseline. For eGFR the relative change will be displayed in addition to the absolute change from baseline.

Summary statistics for serum potassium, eGFR, and serum creatinine will also be repeated by treatment group and visit separately for each level of the stratification factors (region and LVEF).

The following special safety parameters will be further assessed by displaying the number and percentage of patients with safety events as described below by treatment group, visit, and for

any time on treatment (including unscheduled assessments) and until 3 days after last study intervention administration. This will also be performed by stratification factors. The summaries will be provided for the number and percentage of patients with:

- Absolute value of serum potassium >5.0 mmol/L, ≥5.5 mmol/L and ≥6 mmol/L
- Relative decrease from baseline in eGFR of ≥25%, ≥30%, ≥40%, ≥50% and ≥57%
- Absolute value of eGFR <30 mL/min/1.73 m²
- Increase from baseline in serum creatinine >0.3 mg/dL and >0.5 mg/dL.

The percentage of patients with the respective events (non-stratified) at any time on treatment (including unscheduled assessments) and until 3 days after last study intervention administration will be compared between the finerenone and placebo groups by applying separate exploratory χ^2 tests with continuity correction. If the expected number of patients in at least 1 cell of the 2x2 contingency table is <5, Fisher's exact test will be applied instead of the χ^2 test. Estimates and two-sided 95% confidence intervals will be provided for each treatment group and the treatment differences. Clopper-Pearson confidence intervals will be calculated for each treatment group, while for treatment differences the exact unconditional confidence limits will be calculated.

9.5 Interim Analyses

One non-binding interim analysis for futility is planned when approximately 30% of the required total number of primary endpoint events have been observed. If the observed rate ratio on the primary endpoint is above 0.95, the trial is planned to be stopped for futility. This gives a probability of approximately 69% to stop under the null hypothesis (i.e. no treatment effect on the composite of HHFs and CV deaths) and leads to a loss in power of less than 1% under the alternative hypothesis of the treatment effect assumed for the sample size determination. No adjustment for this loss in power will be made.

The futility analysis is considered to be non-binding, the DMC will be asked to also consider important secondary efficacy endpoints as well as safety in their assessment.

In addition, one formal interim analysis for efficacy is planned when approximately 2/3 of the required total number of primary endpoint events have been observed.

If the interim analysis shows clear and consistent benefit in the finerenone treatment group, the DMC may recommend early study termination. The Haybittle-Peto rule will be used to guide the decision regarding early stopping of the study for success: a reduction of 3 standard deviations (of the test statistic) in the analysis of the primary efficacy endpoint (two-sided p-value <0.0027) at the interim analysis. In addition, a nominal significant effect on CV death component should be present (two-sided p-value<0.05) at the interim analysis. Note: The criterion for CV death would not be considered to prove formal statistical significance, as it does not keep the alpha level. It has been added so that the trial is only stopped at the interim if there is at least a certain amount of evidence of a beneficial treatment effect on CV death.

If the study doesn't stop for overwhelming efficacy at the interim analysis, a small adjustment to the alpha level at the final analysis is required to preserve the overall type I error rate of 5%. For an information fraction of 2/3, the adjusted alpha level of 4.967% applies. If the study is not stopped early for success a p-value of p<0.04967 is therefore required at the final analysis to achieve formal statistical significance. No alteration to the sample size is done to

account for this adjustment in significance level with negligible loss in power under the alternative hypothesis.

The sponsor will oversee and discuss with the Steering Committee overall blinded event rates to ensure that they are in line with protocol assumptions. If overall event rates are lower than expected, consideration will be given to altering the study design, such as increasing the sample size or extending the study duration without knowledge of any treatment effect.

The non-binding futility interim analysis as well as the efficacy interim analysis will be conducted such that the ongoing study integrity is maintained. Only the independent statistical support group, who is responsible for providing the interim analyses results to the independent data monitoring committee (DMC) will be unblinded to the individual treatment group assignments. Interim analyses results will not be shared with investigators, participants, or the study team who are involved with the conduct of the study, nor will be available for submission before the final database lock. An interim analysis SAP will describe the planned interim analyses in greater detail.

9.6 Data Monitoring Committee (DMC)

Ongoing safety monitoring during the conduct of the study will be performed by an external and independent DMC. An independent statistical analysis center (SAC) will be involved in processing unblinded safety data for the DMC. Analysis periods and procedures will be defined in an operational charter (DMC charter) filed in the study file.

Outcome events as defined in Section 8.3.6 will not be reported as AEs or SAEs by the investigators; however, they will be collected in the eCRF. The independent DMC will periodically review and assess all outcome events as well as safety data from the study for imbalances in safety outcomes in an unblinded manner. It is believed that in this way, patient safety can continue to be monitored throughout the duration of the trial, and the integrity of the study maintained. If unexpected safety issues are identified, specific amendments will be implemented based on the recommendation of the DMC.

Following data review, the DMC will provide written recommendations that will be transferred to the chairmen of the Steering Committee and Bayer. DMC opinions and recommendations will be notified by Bayer as soon as possible to the competent authorities and the IECs where they qualify for expedited reporting.

10.Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 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 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines:
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g. 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 amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Any substantial modification of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH Good Clinical Practice and national and international regulations.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements, ICH guidelines, the IRB/IEC, and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor 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 course of the study and for one year after completion of the study.

10.1.3 Informed Consent Process

The investigator or his/her qualified representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance

Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented 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 authorized representative.

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

10.1.4 Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor 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 his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees Structure

Clinical Event Committee (CEC)

The main task of the CEC, which is composed of a panel of experts in cardiology and nephrology, is to adjudicate all HHFs, HF equivalents and all deaths. The committee will be provided with all relevant documentation related to the event.

The procedures followed by the committee will be specified in the CEC charter. Adjudication results will be the basis for the final analysis.

Data Monitoring Committee (DMC)

Ongoing safety monitoring during the conduct of the study will be performed by an independent external and unblinded DMC (see Section 9.6). Analysis periods and procedures will be defined in the DMC charter and filed in the electronic trial master file. Following data review, the DMC will provide written recommendations that will be transferred to Bayer and the Steering Committee chair. All other definitions will be provided in the DMC charter.

10.1.6 Dissemination of Clinical Study Data

Result summaries of Bayer's sponsored clinical trials in drug development Phases 2, 3, and 4 and Phase 1 studies in participants are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "*Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases*". In addition, results of clinical drug

trials will be provided on the publicly funded website www.ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.

Bayer commits to sharing upon request from qualified scientific and medical researchers participant-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in participants for medicines and indications approved in the United States (US) and European Union (EU) on or after 01 JAN 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g. 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 provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g. Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized 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 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor.
  No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 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.
- The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this. It is the expectation of the sponsor that all data have source documentation available at the site.
- Data reported on the CRF or 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 can be found in ICH-GCP guidelines E6(R2) § 1.51, 1.52.

10.1.9 Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. 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 the sponsor or 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, the sponsor'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, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(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.

10.1.10 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 the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual

site data. In this case, a coordinating investigator will be designated by mutual agreement.

- In addition, the sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10–1 will be performed by the central laboratory.
- In addition to samples for the central laboratory, other blood safety samples will be taken from the Screening Visit onwards for analysis at the local laboratory. These samples will be taken only as long as the participant has not prematurely and permanently discontinued study intervention. From visit 2 (Month 1) onwards, study participants may have their local laboratory tests taken up to 3 days prior to the study visit.
- eGFR (CKD-EPI) (Horio et al. 2010, Levey et al. 2009) must be measured/calculated locally for as long as the participant is treated with the study intervention
- Up-titration or down-titration of the study intervention will be based on local potassium and must be documented in the eCRF. Down-titration of the study intervention will occur for safety reasons only.
- Potassium values should be recorded using a single decimal point (e.g. 4.5 mmol/L or mEq/L). In the event of hyperkalemia, please see Section 6.6.1 for guidance on treatment.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing. Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.

Table 10–1 Protocol-Required Clinical/Safety Laboratory Assessments

Parameter	Component
Hematology	White blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hb), hematocrit, platelets, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), red cell distribution width (RDW)
Clinical chemistry (full)	Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), creatinine kinase (CK), serum creatinine, eGFR (CKD-EPI (Horio et al. 2010, Levey et al. 2009), blood urea nitrogen, bilirubin (fractionated), sodium, serum potassium
Glycated hemoglobin	HbA1c
Urinalysis	Urinary albumin-to-creatinine ratio (UACR)
Biomarkers	N-terminal prohormone B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin-t (hs-TnT)

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.
- Events related to study-required procedures (e.g. invasive procedures, side effects caused by change of concomitant medication to fulfil study eligibility).

Events <u>NOT</u> Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy) that is not required by the study protocol as outlined by the SoA: the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or

convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

- The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE/SAE CRF pages.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated safety-relevant SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection transmission (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).
- Contacts for SAE reporting can be found in in the investigator site file.

SAE Reporting to the Sponsor via Paper CRF

- Email transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor.
- In rare circumstances and if email transmission is not feasible, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the investigator site file.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (e.g. mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female.
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

According to pre-clinical and clinical data, Finerenone does not indicate teratogenicity/ fetotoxicity in early pregnancy (please refer to the Investigator's Brochure for details). Based on these data, women of child-bearing potential can be included into the trial if reliable contraception is used.

Contraception should be used until 30 days after last intake of study intervention.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥ 1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c.) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. d) Considered effective, but not highly effective – failure rate of ≥ 1% per year. Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

Male participants do not have to use condoms in the study, because there is no indication of male-mediated developmental toxicity. Therefore, female partners of male participants are also not required to use contraception.

Collection of Pregnancy Information:

Male Participants with Partners who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, after obtaining the signed informed consent from both parents, unless local law or specific circumstances of the respective case allow otherwise, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
  - While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
  - A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.5 Appendix 5: Definitions of Clinical Events

General clinical event definitions are based on Hicks`s criteria (Hicks et al. 2018) of each component of the primary composite endpoint and can be found below. Further details of all endpoint definitions and its criteria will be provided in the Endpoint Manual and CEC Charter.

10.5.1 Heart Failure (HF) Events

HF events include HHF as well as urgent HF visits. All HF events are to be captured on the eCRF.

10.5.1.1 Heart Failure Hospitalization (HHF)

- An HHF is defined as an event in which the participant is admitted to the hospital with a primary diagnosis of HF. The length of stay is **at least 24h** (or a change in calendar date if the hospital admission and discharge times are unavailable). The participant exhibits new or worsening symptoms of HF on presentation, has objective evidence of new or worsening HF (physical examination findings and/or laboratory criterion) and receives initiation or intensification of treatment specifically for HF.

10.5.1.2 Urgent Heart Failure (HF) Visits

- An urgent HF visit is defined as an event in which the participant has an urgent, unscheduled office/practice or Emergency Room visit for a primary diagnosis of HF, but not meeting the criteria for a HHF. The participant is not admitted to the hospital and exhibits new or worsening symptoms of HF (physical examination findings and/or laboratory criterion) and receives initiation of intravenous diuretic or vasoactive agent or mechanical or surgical intervention (see Endpoint Manual for details). Of note, significant augmentation of oral diuretic therapy will NOT be enough to fulfill the urgent HF visit criteria
- General consideration (urgent HF visits): Clinic visits for **scheduled** administration of HF therapies or procedures (e.g. intravenous diuretics, intravenous vasoactive agents or mechanical fluid removal) do NOT qualify as non-hospitalized HF events.

10.5.2 Cardiovascular (CV) Death

CV death includes any death resulting from an acute myocardial infarction, sudden cardiac death, sudden death, death due to HF, death due to stroke, death due to CV procedures, death due to CV hemorrhage, and death due to other CV causes.

10.6 Appendix 6: Country-Specific Requirements

Country-specific requirements will be outlined in local amendments.

10.7 Appendix 7: Calculating the Child Pugh score

The severity of liver disease (Table 10–2) will determine the Child Pugh score (Table 10–3).

Table 10–2 Grading of Severity of Liver Disease, Adapted from (Pugh et al. 1973)

Factor	+1	+2	+3
Bilirubin (mg/dL)	<2	2 – 3	>3
Albumin (g/dL)	>3.5	2.8 – 3.5	<2.8
International Normalized Ratio	<1.7	1.7 – 2.3	>2.3
Ascites	None	Mild	Moderate / Severe
Encephalopathy	None	Grade I - II	Grade III – IV

Table 10–3 Classification Using the Added Score from Table 10–2, Adapted from (Pugh et al. 1973)

Child-Pugh Class	A	B	C
Points	5 – 6	7 – 9	10 – 15

10.8 Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment (number 2) is located directly before the table of contents (TOC).

Overall Rationale for all Protocol Amendments

Type of Protocol Amendment	Numbering/ Identifier	Type of change(s)
Global	Amendment 2	To alter certain efficacy endpoints of the study, add clarity and correct inconsistencies. For details, see Protocol Summary of Changes Table on page 2 of this document.
Country-specific	IND-2	To comply with Indian regulatory requirements, details and clarity were added to unblinding procedures for SUSARs that derive from disease-related outcome events.
Country-specific	JPN-2	To account for modifications in Amendment 1 while complying with Japanese regulatory requirements on reporting of disease-related outcome events in Japan (introduced in JPN-1).
Country-specific	CHN-2	To address constraints of SARS-CoV-2 serology testing in China, serology test was removed in some sections of the protocol.
Country-specific	IND-1	To comply with Indian regulatory requirements, the protocol was revised to require the documentation of all disease-related outcome events in India which are to be reported as (S)AEs.
Country-specific	LTU-1	To comply with Lithuanian regulatory requirements, the protocol was revised to include the evaluation of LVEF and structural heart abnormalities at least within 90 days prior to randomization.
Global	Amendment 1	To address the requests from health authorities, add clarity and correct inconsistencies. For details, see Section 10.8.1.
Country-specific	USA-1	To implement the decentralized clinical trial (DCT) model in 10-20% of selected study sites in the US. To ensure clear and easy instructions, an integrated protocol (instead of a stand-alone amendment) was prepared.
Country-specific	SVK-1	To comply with Slovakian regulatory requirements, additional pregnancy testing was required for certain study visits.
Country-specific	GBR-1	To include erythromycin, a moderate CYP3A4 inhibitor, in the list of concomitant therapies that are not permitted during treatment with study intervention.
Country-specific	JPN-1	To add the use of the Japanese modification of the CKD-EPI equation in study sites in Japan, and to comply with Japanese regulatory requirements, the protocol was revisesd to require the documentation of certain disease-related outcome events in Japan which are to be reported as (S)AEs.
Country-specific	CHN-1	To exclude explorative biomarker assessments **except** for the biomarkers NT-proBNP and hs-TnT in patients in China,.

10.8.1 Amendment number 1: 21 SEP 2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union

Overall Rationale for the Amendment:

This amendment was made to address the requests from health authorities. In addition, more clarity has been provided and inconsistencies were corrected.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA) 8.2.3 Clinical Safety Laboratory Assessments 10.2 Appendix 2: Clinical Laboratory Tests	SARS-CoV-2 serology to be conducted at baseline and then annually was added.	General regulatory guidance to collect SARS-CoV-2 data
1.3 Schedule of Activities (SoA)	Clarification of “applicable to selected sites only” was added to PGIC and PGIS.	Additional clarification needed
1.3 Schedule of Activities (SoA) 8.2.3 Clinical Safety Laboratory Assessments	Biomarkers NT-proBNP and hs-TnT added as separate line in the SoA as they will be assessed less frequently	To align with schedule of trials in similar populations
1.3 Schedule of Activities (SoA) 8.2.3 Clinical Safety Laboratory Assessments 10.2 Appendix 2: Clinical Laboratory Tests	The time period of local laboratory assessments from visit 2 (Month 1) onwards was changed to up to 3 days prior to the study visit.	To accomodate site requests to reduce patient burden to wait for lab results during the visit
1.3 Schedule of Activities (SoA) 8.5 Pharmacokinetics	The timing of the PK sample to be taken at Visit 6 (Month 12) and Month 20 and every 8 months was changed to 1.5-10 hours during the visit after study intervention intake at home.	To optimize PK collection scheduling based on previous experience
1.3 Schedule of Activities (SoA) 8.5 Pharmacokinetics	The possiblity to postpone the PK trough sample from Visit 3 to Visit 4 or 5, if e.g. participants took study medication at home on the day of Visit 3, was added.	To accomodate site requests to provide some flexibility
5.1 Inclusion Criteria	Inclusion criterion #3 has been reworded: On diuretic treatment for at least 30 days prior to randomization	To avoid confusion and exclude occasional diuretic use
5.2 Exclusion criteria	Exclusion criterion #24 was changed to include erythromycin to the list of non-permitted concomitant therapy.	To keep protocol consistent with the IB.
6.3 Measures to Minimize Bias: Randomization and Blinding	Pharmacokinetic and exposure-response analyses were added.	Standard procedure omitted by error in the first version
6.5 Prior and Concomitant Therapy	Erythromycin was added to the list of concomitant treatments not permitted during treatment with study intervention.	To keep protocol consistent with the IB.
6.5 Prior and Concomitant Therapy	Examples of BCRP/OATP substrates were deleted.	To avoid confusion. A list of BCRP/OATP substrates will be provided and updated when needed.
7.1 Discontinuation of Study Intervention	Initiation of treatment with an MRA was changed to a criterion for the premature and permanent discontinuation of the study intervention.	To be consistent with other sections in the protocol (Section 6.5) and clarify that concomitant use with an MRA is prohibited.
8.1 Efficacy Assessments	The possibility for the questionnaires to be read to the participant and answers completed by a delegated person in limited circumstances was added.	To avoid missing questionnaire data.
8.1.3 Patient Global Impression of Change (PGIC) and Severity (PGIS)	The content of the 2 PGI questionnaires were added.	Updated based on feedback from regulatory authority
8.3.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs	The definition and handling of the disease related events were updated.	Section updated as figure was leading to confusion.
8.5 Pharmacokinetics	Details on the analyses of the plasma concentration versus time data were added.	Details missed by error in previous version
9.1 Statistical Hypotheses 9.4.1.2 Secondary Efficacy Variables	Details on the significance level were added and referred to Section 9.5.	Full details regarding adjustment of significance level added to Section 9.5 in response to ethics

Section # and Name	Description of Change	Brief Rationale
		committee comment
9.3 Populations for Analyses	Definition of the pharmacokinetic analysis set (PKS) was added.	Included for completeness
9.4 Statistical Analyses	Stated that the impact of COVID-19 will be addressed in the SAP.	Included for completeness
9.4.1.1 Primary Efficacy Variable 9.4.1.2 Secondary Efficacy Variables	Statement that events to be evaluated by the CEC was updated to those could potentially fulfill the criteria for primary efficacy variables during the study and was moved from Section 9.4.1.2 to 9.4.1.1.	Included for completeness. Statement relevant to primary efficacy variables (not secondary)
9.4.1.2 Secondary Efficacy Variables	Details on the significance level for testing secondary endpoints and components of the primary endpoint were updated.	Updated for clarity – original statement that testing will be conducted at „full level of alpha“ was ambiguous
9.4.1.2 Secondary Efficacy Variables	Details on the components of the renal endpoint were updated.	Updated based on feedback from regulatory agency
9.4.1.2 Secondary Efficacy Variables	Details on the subgroups of the hospitalizations for heart failure (HHF) were updated.	Updated to be consistent with data collection in RAVE
9.4.1.3 Exploratory Variables	Details on the analyses of the total number of CV hospitalizations, all-cause hospitalizations, and the change from baseline in NYHA class were added.	Included from the SAP for completeness
9.5 Interim Analyses	Details on the futility analyses and the alpha level and associated power loss at the final analysis if the study doesn't stop for overwhelming efficacy at the interim analysis were added.	Updated based on feedback from Ethics Committee
10.1.7 Data Quality Assurance	The length of time for the records and documents, including signed ICFs, pertaining to the conduct of this study to be retained by the investigator was changed to 15 years after study completion unless local regulations or institutional policies require a longer retention period.	To align with current regulations the duration was updated to 15 years

In addition, editorial and administrative changes have been made throughout the document.

10.9 Appendix 8: Abbreviations

ACC/AHA	American College of Cardiology/American Heart Association
ACEI	angiotensin-converting enzyme inhibitor
ACM	all-cause mortality
AE	adverse event
ALDO-DHF	Aldosterone Receptor Blockade in Diastolic Heart Failure
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	alkaline phosphatase
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
ARTS	Mineralocorticoid Receptor Antagonist Tolerability Study
ARTS-DN	Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy
ARTS-HF	Mineralocorticoid Receptor Antagonist Tolerability Study–Heart Failure
AST	aspartate aminotransferase
AUC	area-under-the-curve
BMI	body mass index
BNP	B-type natriuretic peptide
CEC	Clinical Event Committee
CFR	Code of Federal Regulations
CHARM	Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity
CHARM-Preserved	Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity
CHF	chronic heart failure
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease of 2019
CRF	case report form
CV	cardiovascular
CVD	cardiovascular death
CYP3A4	cytochrome P450 isoenzyme 3A4
DAOH	days alive and out of hospital
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
DREs	Disease related events
ECG	electrocardiogram
eCRF	electronic case report form

eGFR	estimated glomerular filtration rate
EPHESUS	Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
ESC	European Society of Cardiology
EOS	end-of-study (visit)
EQ-5D-5L	EuroQol Group 5-dimension, 5-level questionnaire
EQ VAS	EuroQol visual analogue scale
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EuroQoL	European Quality of Life (scale)
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GWTG-HF	Get With the Guidelines - Heart Failure
HbA1c	glycated hemoglobin
HF	heart failure
HFmrEF	HF with mid-range EF
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced EF
HHF	hospitalization for heart failure
HR	hazard ratio
HRT	hormone replacement therapy
hs-TnT	high-senstivity troponin-t
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IR	immediate release
IV	intravenous
IxRS	interactive voice / web response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAA	left atrial area
LAD	left atrial diameter
LAVI	left atrial volume index
LVEF	left ventricular ejection fraction
LVMI	left ventricular mass index
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities

MR	mineralocorticoid receptor
MRA	mineralocorticoid receptor antagonist
NONMEM	non-linear mixed effect modeling
NP	natriuretic peptide
NSAID	non-steroidal anti-inflammatory drug
NT-proBNP	n-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
OD	once daily
PARAGON-HF	Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction
PD	premature discontinuation
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetics
PKS	pharmacokinetic analysis set
PT	post-treatment (visit)
RAAM-pEF	Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction
RAAS	renin-angiotensin aldosterone system
RALES	Randomized Aldactone Evaluation Study
RAVE	electronic data capturing system
RDW	red cell distribution width
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SBP	systolic blood pressure
SGLT	sodium glucose transport protein
SoA	schedule of activities
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
T2D	type 2 diabetes
TEAE	treatment-emergent adverse event
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial
TSS	Total Symptom Score
UACR	urinary albumin-to-creatinine ratio
US(A)	United States (of America)
WOCBP	women of child-bearing potential

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Title Page

A multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of finerenone on morbidity and mortality in participants with heart failure (NYHA II-IV) and left ventricular ejection fraction ⩾ 40% (LVEF ⩾ 40%)

FINEARTS-HF: **FIN**erenone trial to investigate **E**fficacy and s**A**fety superio**R** to placebo in pa**T**ient**S** with **H**eart **F**ailure

Bayer study drug	Finerenone / BAY 94-8862		
Study purpose:	Efficacy and safety		
Clinical study phase:	III	**Date:**	04 SEP 2020
Study No.:	20103	**Version:**	1.0
Authors:	PPD PPD PPD PPD PPD PPD PPD PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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Abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
ACM	All-cause mortality
AE	Adverse event
ANCOVA	Analysis of covariance
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
ATC	Anatomical therapeutic chemical
BCPR	Breast Cancer Resistance Protein
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass graft
CEC	Clinical event committee
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLIPS	Clinical Pharmacology Standards
COPD	Chronic obstructive pulmonary disease
CSR	Clinical study report
CSS	Clinical Summary Score
CoV	Coefficient of Variation
CV	Cardiovascular
CYP3A4	Cytochrome P450 isoenzyme 3A4
DAOH	Days alive and out of hospital
DBP	Diastolic blood pressure
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EoS	End of study
EQ VAS	EuroQol Group visual analogue scale
EQ-5D-5L	EuroQol Group 5-dimension, 5-level questionnaire
FAS	Full analysis set
GCP	Good clinical practice
HF	Heart failure
HHF	Hospitalization for heart failure
HR	Hazard ratio
hs-TNT	High sensitive troponin T
ICF	Informed consent form
ICH	International Council for Harmonisation
ITT	Intention-to-treat
K	(Serum/plasma) potassium
KCCQ	Kansas City Cardiomyopathy Questionnaire
LLOQ	Lower limit of quantification
LVEF	Left ventricular ejection fraction
LWYY	Lin, Wei, Yang and Ying
MedDRA	Medical Dictionary for Regulatory Activities
MLG	MedDRA labeling groupings
MRA	Mineralocorticoid receptor antagonist
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
OATP	Organic anion transporting polypeptides
OD	Once daily
OSS	Overall Summary Score
PBMQ	Project-specific Bayer MedDRA Queries
PCI	Percutaneous coronary intervention

PD	Pharmacodynamic
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic
PLS	Physical Limitation Score
PT	Preferred term
RR	Rate ratio
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SFS	Symptom Frequency Score
SGLT-2	Sodium-glucose transport proteins-2
SMQs	Standardized MedDRA queries
SOC	System organ class
T2D	Type 2 diabetes
TEAE	Treatment emergent adverse event
TIA	Transitory ischemic attack
TLFs	Tables, Listings and Figures
TSS	Total Symptom Score
UACR	Urinary albumin-to-creatinine ratio
ULOQ	Upper limit of quantification
WHO-DD	World Health Organization Drug Dictionary

1. Introduction

This Statistical Analysis Plan (SAP) is based on the following document(s):

Clinical Study Protocol 20103 version 1.0 dated 05 MAR 2020

This SAP describes the statistical analysis of the double-blind placebo-controlled study treatment phase. An independent data monitoring committee (DMC) will be involved in the review of data for safety and efficacy as will be described in the DMC Charter. Blinded adjudication of clinical outcomes will be performed by an independent Clinical Event Committee (CEC), as will be described in the CEC Charter.

2. Study Objectives

Please refer to the study protocol for details on finerenone and on heart failure.

Study 20103 will be the first large-scale, long-term outcome study investigating the efficacy and safety of the non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone on morbidity and mortality in participants with heart failure (New York Heart Association [NYHA] class II-IV) and left ventricular ejection fraction ≥40% (LVEF ≥40%), in comparison to placebo and in addition to standard-of-care therapy for congestion and comorbidities. Primary endpoint includes Cardiovascular (CV) death and total (first and recurrent) heart failure (HF) events (hospitalizations for heart failure [HHF] or urgent HF visits) in HF patients (NYHA class II–IV) and LVEF ≥40%. Secondary endpoints will include: change from baseline to Month 6, 9 and 12 in total symptom score (TSS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ); time to first occurrence of composite renal endpoint: sustained decrease in estimated glomerular filtration rate (eGFR) ≥40% relative to baseline over at least 4 weeks, or sustained eGFR decline <15ml/min/1.73m^2 or initiation of dialysis or renal transplantation; time to all-cause mortality (ACM); and the safety and tolerability of finerenone.

An inappropriate release of aldosterone contributes to target organ damage found in HF, myocardial infarction, chronic renal failure, and hypertension. The extensive expression of the mineralocorticoid receptor (MR) in the CV and renal systems, including the heart, endothelial cells, vascular smooth muscle cells, and kidney mesangial cells, provides further evidence for the role of aldosterone in CV and renal injury.

Blockade of the action of aldosterone and potentially other MR ligands such as cortisol has been demonstrated to be of benefit in HF (Pitt et al. 1999, Zannad et al. 2010). Results from a short-term Phase IIb study (ARTS-HF Study 14564) suggest that treatment with finerenone in addition to standard therapy for HF with LVEF ≤40% improves mortality and CV morbidity outcomes; however, long-term outcome conclusive studies examining whether MRAs can prevent CV events are still lacking in this patient population. Study 20103 will be the first study to address these questions in the HF with LVEF ≥40% population.

Finerenone also has the potential to address the unmet medical needs in patients with type 2 diabetes (T2D) and clinical diagnosis of chronic kidney disease (CKD). The Phase III program with finerenone in patients with T2D and clinical diagnosis of CKD encompasses 2 placebo-controlled, large-scale, long-term outcome trials: Study 16244, the first large-scale, long-term outcome trial that examined whether finerenone can slow the progression of kidney disease and Study 17530 which is examining the effects of finerenone on CV outcomes.

3. Study Design

Study 20103 is a randomized, double-blind, parallel-group, placebo-controlled, multicenter, event-driven Phase III study with independently adjudicated clinical outcome assessments. This study will be conducted in patients with HF and LVEF ≥40%. The overall study design is displayed in Figure 3–1.

Participants will be randomized in a 1:1 ratio to either finerenone or placebo. The study is designed to be able to show an effect on the primary endpoint with a power of 90% at an alpha level of 5%. It is anticipated that 5500 participants will be randomized and approximately 6900 will be screened (screening failure rate of approximately 20%). A total of approximately 2375 total (first and recurrent) primary composite events are targeted.

The anticipated duration of the study will be approximately 42 months, with a recruitment period of 24 months. However, as an event-driven study, the actual length of the study will depend on the observed event rates, the participant recruitment rate, and the length of the recruitment period.

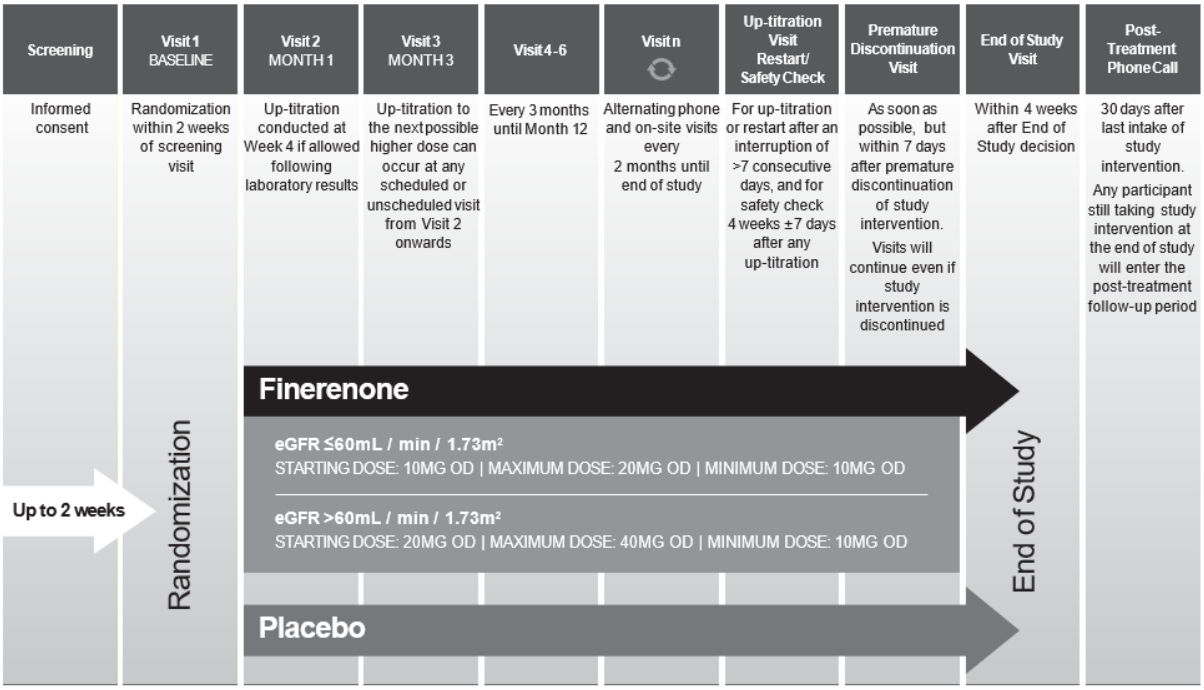
Enrolment in the trial may be capped based on the proportion of patients in certain LVEF categories, in each NYHA class, with/without atrial fibrillation, and by geographic region, among other variables, to ensure recruitment of a representative study population.

The randomization will be stratified by country/region and baseline LVEF (<60%, ≥60%).

Since all randomized participants belong to the Full Analysis Set (FAS) on which the efficacy analyses are based, it is important to avoid randomization of non-eligible patients into the study.

The general study design as applied to this study is shown in Figure 3–1. There is a screening period, a double-blind treatment period and a safety follow-up period. Patients prematurely terminating from the study and up to the primary study completion will be asked to attend scheduled visits to collect efficacy data.

Figure 3–1: Study design



Screening Visit

After providing written informed consent, a Screening Visit to confirm the participant's eligibility will take place prior to randomization. The Screening Visit may take place on the same day as randomization (Visit 1).

Treatment Period

Following a screening period of up to 2 weeks, eligible participants will be randomized in a 1:1 ratio to either finerenone or placebo. Participants with an eGFR ≤60 mL/min/1.73 m² measured at baseline will start with 10 mg once daily (OD) (**dose level 1**) with a maximum maintenance dose of 20 mg OD (**dose level 2**), whereas participants with an eGFR >60mL/min/1.73 m² measured at baseline will start with 20 mg OD (dose level 2) with a maximum maintenance dose of 40 mg OD (**dose level 3**).

There will be at least 2 scheduled visits within the first 3 months from randomization: Visit 2 will take place after 1 month and Visit 3 will take place 3 months after randomization; thereafter, scheduled visits will occur every 3 months until Visit 6 at Month 12. After 1 year from randomization, telephone contact visits will take place at Month 14 and from then onwards every 4 months (i.e. Month 18, Month 22, etc.) alternating with on-site visits (i.e. Month 16, Month 20, etc.) until the end of the study is reached.

Up-titration is expected to occur after 4 weeks ± 7 days of treatment at Visit 2 (Month 1). Ideally, each participant will be on the maximum maintenance dose at this point. In the event of elevated potassium values, participants will be down-titrated to the next lower dose. Down-titrations can be performed at any time after the start of study intervention treatment, at any scheduled or unscheduled visit. At any scheduled or unscheduled visit, the dose of study intervention may be increased to the next possible higher dose, based on serum/plasma potassium level and provided the participant was already on a stable dose for 4 weeks ± 7 days.

Participants will attend an additional unscheduled safety visit 4 weeks ± 7 days after each up-titration; potassium levels and renal function will be monitored at this safety visit. In addition to the protocol-specified visits, participants may be seen at any time throughout the study at the discretion of the investigator.

Any changes in the study intervention dose, including interruption/permanent discontinuation or restart of study intervention, must be recorded in the electronic case report form (eCRF).

It is planned that all randomized participants will remain in the study until either:

a. an instruction is received from the sponsor after the targeted number of primary endpoint events have occurred
   or
b. the study is terminated prematurely at the recommendation of the independent DMC.

After randomization, study intervention discontinuation does not constitute the participant's withdrawal from the study, and all participants should continue to be followed up. All randomized participants, including any participant who experiences an event considered for the pre-specified primary or secondary endpoints, should continue to receive double-blinded treatment until the study is completed, provided there are no safety grounds for discontinuing treatment.

Post-treatment Follow-up Period

The period between a participant's last intake of study intervention and last visit in the study is referred to as the 'post-treatment follow-up period'.

In case of premature discontinuation of study intervention, participants are expected to continue to attend all protocol-specified study visits, and are expected to perform all scheduled assessments as described in the Premature Discontinuation Schedule of Assessment in the protocol.

Any participant still taking study intervention at the point of end of study will enter the post-treatment follow-up period after stopping study intervention at the End of Study (EoS) Visit. For these participants, this phase will last 30 (+5) days, and will end upon completion of the Post-Treatment Visit (a telephone call visit).

The **primary objective** of this study is to:

- Demonstrate the superiority of finerenone to placebo in reducing the rate of Cardiovascular (CV) death and total (first and recurrent) HF events (HHF or urgent HF visit) in HF patients (NYHA II–IV) and LVEF ≥40%.

The **secondary objectives** of this study are to:

- Determine the superiority of finerenone to placebo with regard to each of the following:
    - Change from baseline to Month 6, 9 and 12 in TSS from KCCQ
    - Time to first occurrence of composite renal endpoint:

      sustained decrease in eGFR ≥40% relative to baseline over at least 4 weeks, or sustained eGFR decline <15ml/min/1.73m^2 or initiation of dialysis or renal transplantation
    - Time to ACM
- Assess the safety and tolerability of finerenone

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

The analysis will be based on the Global Standard Tables (Version 4.0 or higher) and the Clinical Pharmacology Standards (CLIPS) (Version 1.2 or higher) where appropriate. Compound Standard Tables will be developed.

The validity of subjects for allocation to various analysis sets will be assessed in an ongoing manner in blind review meetings and decisions will be documented in the blind review reports prior to unblinding.

A log-normal distribution is assumed for serum creatinine, urinary albumin-to-creatinine ratio (UACR), and N-terminal prohormone B-type natriuretic peptide (NT-proBNP). For all other metric variables, a normal distribution is assumed. The distributional assumptions will be investigated and if necessary, nonparametric methods or transformation of the data will be considered.

All variables will be analyzed by descriptive statistical methods. The number of data available, mean, standard deviation (SD), minimum, median, and maximum will be calculated for metric data. The geometric mean, SD and coefficient of variation (CoV) will be provided instead of the arithmetic mean and SD for the variables where log-normal distributions are assumed, as follows:

$$CoV = \sqrt{\exp(SD_{ln}^2) - 1}$$

SD_{ln} being the standard deviation of the log-transformed values. Frequency tables will be generated for categorical data.

The laboratory parameter eGFR will be calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Levey et al., 2009) for all analyses specified in this SAP. For patients recruited in Japan, the Japanese formula adjustment will be applied (Horio et al., 2010).

All subjects will be analyzed according to the planned treatment group in FAS per the intention-to-treat (ITT) principle. All subjects will be analyzed according to the actual treatment in the Safety Analysis Set (SAF). If a subject receives both treatments due to a bottle error, the treatment actually received for the majority of the time in the study will be used in SAF.

Only adjudicated outcome events will be used for analysis of the primary and secondary efficacy variables (except for sustained decrease in eGFR ≥40% relative to baseline over at least 4 weeks and sustained eGFR decline <15ml/min/1.73m^2 which will be derived from central laboratory measurements and not be adjudicated); Section 6.2.4 specifies how investigator-reported outcomes for these variables will be summarized. Outcome events for exploratory efficacy variables (e.g. non-fatal myocardial infarction, non-fatal stroke, etc.) will not be adjudicated.

The stratified analyses mentioned in this SAP will be conducted in consideration of the randomization stratification factors:

- LVEF: <60%, ≥60%
- Pooled region: randomization will be stratified by country/region, for the analyses individual countries/regions will be combined into pooled regions as follows:
    - Western Europe and Oceania: Australia, Austria, Denmark, Germany, Israel*, Netherlands, New Zealand, United Kingdom
    - Southwestern Europe: Italy, Portugal, Spain
    - Central Europe: Czechia, Hungary, Poland, Slovakia
    - Southeastern Europe: Bulgaria, Greece, Romania, Turkey
    - Northeastern Europe: Finland, Latvia, Lithuania, Russia, Ukraine
    - Asia: China, Hong Kong, India, Japan, Malaysia, South Korea, Taiwan
    - North America: Canada, United States of America
    - South and Central America: Argentina, Brazil, Colombia, Mexico

*Although not geographically located in Western Europe or Oceania, Israel has been included in this pooled region.

In case of issues (e.g. model convergence) with using these predefined pooled regions at the final analyses, the pooled regions may be further combined. Any such changes will be described in the clinical study report (CSR).

All subjects will be analyzed according to their correct stratification category. In case of a large number of stratification errors (≥5% of all patients in the FAS), the primary analysis will also be repeated based on the stratification category used in the randomization as a sensitivity analysis.

4.2 Handling of Dropouts

A subject who has been randomized and discontinues study participation prematurely for any reason, either during study treatment or during post-treatment follow-up, is defined as a 'dropout', even if no study drug has been taken. Dropouts will not be replaced.

Data from subjects who prematurely terminated the study will be used to the maximum extent possible.

The number of subjects discontinuing the epochs, together with the primary reason for discontinuation, will be summarized as described in Section 6.1.1.

The number of subjects who prematurely discontinue the study and / or study treatment for any reason, as well as the reasons for premature discontinuation of study and / or study treatment, will be reported. Kaplan-Meier plots for "Time to end of study" and "Time to end of study treatment" will be provided.

All dropouts will be evaluated with respect to

- baseline characteristics
- potential differences between the treatment groups in the proportion of patient withdrawals or in the timing of withdrawals
- the reasons for premature discontinuation of study and/or study treatment.

4.3 Handling of Missing Data

All missing or partial data will be presented in the subject data listing as they are recorded on the eCRF.

General Rules

When appropriate, the following rules will be implemented so as not to exclude subjects or observations from statistical analyses due to missing or incomplete data.

Concomitant medications with missing start and stop date but flagged as being ongoing at end of study will be considered to have started prior to study medication start and end after stop of study medication. The start and end reference period will be imputed as "before" for the medication start and as "during/after" for the medication end.

In case of partially missing end dates for interruptions or permanent stop of study medication intake, a 'worst-case' approach will be applied to impute the start and end dates of study medication intake as the earliest and latest possible dates, i.e.:

- first month of the year and/or first day of the month for a partially missing start date, and
- last month of the year and/or last day of the month for a partially missing end date.

If a subject died earlier than the imputed worst study medication end date, the death date will be taken as the study medication end date. However, if these imputations lead to a temporal overlap between different exposure date records, the imputed dates will be adjusted so that no overlap exists and the time on the higher dose is maximized. The date of first exposure to treatment is not expected to be missing as the patients are instructed by the investigator to take their first dose of study drug directly at Visit 1, but in the very rare case that this date is not recorded, it will be imputed according to the rules outlined above for missing start dates, but not earlier than the randomization date.

When only partial dates are available for clinical events in the efficacy analysis, a median imputation rule will be used:

- For example if the day is missing and the month is July, then day 16 is chosen.
- If the number of potential values is even, the lower of the 2 middle numbers is taken. For example, if the day is missing and the month is June, then day 15 is imputed. The same rule applies if the day and month are missing, e.g. if the year is 2017 and the day and month are missing, 2nd July is used.
- In case the range of possible values is further restricted, e.g. because a patient died in the month in which the day is missing, the median in the restricted set of possible values is calculated. For example, if the clinical event occurred in June 2017 and the respective patient died on 11th June 2017, 6th June 2017 is imputed as the date of the clinical event.

In case a death date is completely missing, it will be imputed on the basis of the last known contact when the subject was still alive and the first known contact when the subject was dead (e.g. from the subject health status follow-up page) as the median of these two dates. As above, if the number of potential values is even, the lower of the two middle numbers is taken.

In case both a non-fatal clinical event and death have partially missing dates, then death takes precedence and will be imputed first according to the rules outlined above. This also applies for non-renal and non-CV death.

However, given the importance of an accurate determination of the adjudicated event date in relation to randomization date for the time to event analysis, we would expect a minimal number of such missing dates.

A worst-case approach will be applied for determining whether an adverse event (AE) with partially missing dates is treatment-emergent or not, i.e. if it is possible that the AE start date is within a period of study drug intake +3 days (on or after study treatment start date and on or before study treatment end date + 3 days) then the AE is considered treatment-emergent.

If intensity of the AE is missing, the event will be considered as severe. If the same event is reported as both unrelated and related to the study drug within a subject, the event will be reported as related to study drug. If the drug relationship is missing, the event will be considered as being related to the study drug.

4.4 Interim Analyses and Data Monitoring

One non-binding interim analysis for futility is planned when approximately 30% (~710) of the required total number of primary endpoint events have been observed. If the observed rate ratio (RR) on the primary endpoint is above 0.95, the trial is planned to be stopped for futility. This gives a probability of approximately 69% to stop under the null hypothesis (i.e. no treatment effect on the composite of HHFs and CV deaths) and leads to a loss in power of less

than 1% under the alternative hypothesis of the treatment effect assumed for the sample size determination. No adjustment for this loss in power will be made.

The futility analysis given above is considered to be non-binding, the DMC will be asked to also consider important secondary efficacy endpoints as well as safety in their assessment.

In addition, one formal interim analysis for efficacy is planned when approximately 2/3 (~1580) of the required total number of primary endpoint events have been observed.

If the interim analysis shows clear and consistent benefit in the finerenone treatment group, the DMC may recommend early study termination. The Haybittle-Peto rule will be used to guide the decision regarding early stopping of the study for success: a reduction of 3 standard deviations (of the test statistic) in the analysis of the primary efficacy endpoint (two-sided p-value <0.0027) at the interim analysis. In addition, a nominal significant effect on the CV death component should be present (two-sided p-value<0.05) at the interim analysis. Note: The criterion for CV death would not be considered to prove formal statistical significance, as it does not keep the alpha level. It has been added so that the trial is only stopped at the interim if there is at least a certain amount of evidence of a beneficial treatment effect on CV death.

See Section 4.7for a detailed description of the testing procedure, including an adjustment of the significance level for the interim analysis.

If the study is stopped early, the primary analysis reported in the CSR will consider all events up to the subjects' respective EoS visits as would have been the case if the study had not stopped early. A sensitivity analysis will take all events up to the interim analysis datacut date into consideration. For this sensitivity analysis, censoring dates after the datacut date will be reset to the datacut date. A detailed plan for the routine DMC safety analyses and the interim analysis will be covered in the DMC charter, the analysis planned to be provided to the DMC will be described in a separate SAP with Tables, Listings and Figures (TLFs) attached to the DMC charter. The DMC will review the data in an unblinded manner, both for the routine safety tables and the interim analysis. There are no predefined stopping conditions for the ongoing safety monitoring of this trial. The statistical analysis for the DMC meetings will be performed by an independent statistical analysis center. The sponsor will oversee and discuss with the Steering Committee overall blinded event rates to ensure that they are in line with protocol assumptions. If overall event rates are lower than expected, consideration will be given to altering the study design, such as increasing the sample size or extending the study duration without knowledge of any treatment effect.

4.5 Data Rules

General data rules are described in this section, further data rules for specific parameters or analyses are specified in the respective subsections of Section 6.

4.5.1 Baseline Values

Baseline values will be defined as the last non-missing measurement before or on the day of randomization. If the last observation available prior to randomization is the measurement from the Screening Visit, this would be used as the baseline value. This also includes assessments from a local laboratory, if no assessment from the central laboratory prior to first intake of study drug is available. Otherwise baseline will be missing.

If more than one measurement was planned for a scheduled time point, for example blood pressure (BP) measurements and heart rate, the mean value of the last set of measurements per

time point prior to randomization will be used as the baseline value. In case of repeated measurements for pre-treatment visits and Visit 1 (Day 1; baseline), the closest measurement prior to the randomization will be used for analysis instead of the scheduled measurements.

When the Screening and Baseline visits are performed on the same day for a participant, the following assessments (scheduled to be performed at both the Screening and Baseline visits) will only be performed once and the data will appear under Screening:

- NYHA class
- Vital signs
- Local lab potassium and creatinine
- Pregnancy test

Where necessary, these data will be considered in the derivation of baseline values per the rules above.

4.5.2 Change from Baseline

Change from baseline will in general be displayed as absolute change from baseline defined as the difference to baseline, i.e.:

Absolute change = Post baseline value – baseline value.

Some parameters will be additionally analyzed as relative change defined as

Relative change = 100 * [(post baseline value – baseline value) / baseline value].

For specific analyses, the relative decrease of a variable will be analyzed instead of the relative change. The relative decrease is equivalent to the negative of the relative change and defined as

Relative decrease = 100 * [(baseline value – post baseline value) / baseline value].

4.5.3 Time Window for Efficacy Events

Events for time to first / recurrent analyses (e.g. primary efficacy endpoint) will be counted from the day of randomization (planned at Visit 1) onwards until the EoS visit following the study termination decision, or until the date of EoS notification + 4 weeks, if the EoS visit has not been performed. In the event of premature discontinuation from the study with no subsequent follow-up information, events will be counted up to the day of the last visit when information on the component is available.

4.5.4 Annual Rate of Recurrent Events

The annual rate of a recurrent event for an individual patient is calculated as:

Annual rate = (Total number of events) / (Follow-up time (days) / 365.25)

4.5.5 Other Data Handling

Data provided by the local laboratory for eGFR will be used for analysis and frequency tables will be provided. In other cases, only the data provided by the central laboratory will be used for analysis; values from local laboratories will not be used in the statistical analysis unless otherwise specified and will be listed only. For example, as described above, local values will be used in the derivation of baseline, if no central measurement is available.

At all visits post-randomization and if not stated otherwise, only the values at scheduled measurements will be used for analysis.

For the derived visit "Any time post baseline" (applicable for efficacy) this will include any measurement after randomization, including unscheduled assessments. For the derived visit "Any time on treatment" (applicable for efficacy and safety), only assessments on or after study medication start date until 3 days after last study drug administration, including unscheduled assessments, will be considered.

For values which are < LLOQ (Lower limit of quantification), half the value of the LLOQ will be used for analysis. Differences between two values < LLOQ will be assigned values of 0. Ratios between two values < LLOQ will be assigned a value of 1. For values which are > ULOQ (Upper limit of quantification), the ULOQ will be used for analysis.

In case of log-normally distributed data, descriptive statistics other than minimum, maximum and median will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification. In tables showing descriptive statistics, where values below LLOQ are included, these descriptive statistics will be marked.

4.5.6 Subgroup Analyses

Exploratory subgroup analysis will be done for the primary and secondary efficacy variables. The subgroup analyses will include the randomization stratification factors. The list of key subgroups (in addition to the stratification factors) and other subgroups analyzed is specified below. Analysis will include descriptive statistics, graphical display of estimated treatment effects with 95% confidence intervals (CIs) in a forest plot and a statistical test for interaction.

Stratification factors

- Pooled region (Western Europe and Oceania, Southwestern Europe, Central Europe, Southeastern Europe, Northeastern Europe, Asia, North America, South and Central America)
- LVEF (<60%, ≥60%)

Key subgroups

- Baseline serum potassium value (≤ 4.5, > 4.5 mmol/L)
- eGFR category at baseline (eGFR 25 to <45, 45 to <60, ≥60 mL/min/1.73 m²)
- Atrial fibrillation at baseline electrocardiogram (ECG) (present, absent)
- Diabetes Mellitus at baseline (present, absent)
- HHF (very recent (≤ 7 days before randomization), recent (>7 days – ≤ 3 months), > 3 - ≤ 6 months, > 6 - ≤ 9 months, >9 - ≤ 12 months, >12 months to ≤ 2 years, >2 years, no index).

Other subgroups

- Race (white, black, Asian, other)
- Sex (male, female)
- Age (40 to ≤65 years, >65 to ≤75 years, and >75 years)
- Baseline body mass index (BMI) (<18.5, ≥18.5 to <25, ≥25 to 30, ≥30 to <35, ≥35 kg/m^2)

- Baseline weight (<60, 60 to <90, ≥90 kg)
- Systolic blood pressure (SBP) at baseline (90 to <130 mmHg, 130 to <160 mmHg, and ≥160 mmHg)
- History of prior MRA use (yes, no)
- Angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) at baseline (yes, no)
- Beta-blocker at baseline (yes, no)
- Diuretic at baseline (yes, no)
- Anti-diabetic treatment at baseline: Insulin and analogues (yes, no)
- Potassium supplementation at baseline (yes, no)
- Potassium lowering agents at baseline (yes, no)
- Potency of concomitant cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitor medication at baseline (strong, unclassified, moderate, weak, none)
- Treatment at baseline with Entresto® (sacubitril/valsartan) (yes, no)
- Treatment with sodium-glucose transport proteins-2 (SGLT-2) (yes, no)
- Prior history of coronary artery disease (yes, no) Baseline waist circumference (normal [men <94cm, women<80cm], increased [men 94-102cm, women 80-88cm], substantially increased [men >102cm, women > 88cm])
- NYHA functional class at baseline (II, III/IV)
- Baseline NT-proBNP: ≤ median and > median
- Baseline hs-TNT: ≤ median vs > median

Individual country analyses, e.g. for Japan, required for regulatory purposes, will be included in a country-specific study SAP.

4.6 Blind Review

The results of the final data assessment will be documented in the final list of important deviations, validity findings and assignment to analysis set(s). Any changes to the statistical analysis prompted by the results of the review of study data will be documented in an amendment and, if applicable, in a supplement to this SAP.

4.7 Testing Procedure and Multiplicity Adjustment

If the interim analysis shows clear and consistent benefit in the finerenone treatment group (defined as two-sided p-value <0.0027 for the primary efficacy endpoint and two-sided p-value <0.05 for the CV death component at the formal interim analysis for efficacy) the DMC may recommend early stopping of the study for success (see Section 4.4 for full details).

If the study is stopped early for success: the final analysis for the primary endpoint will be performed at an overall two-sided significance level of 0.270%. Additionally, the secondary endpoints of:

- Change from baseline to Month 6, 9 and 12 in TSS from KCCQ

- Time to first occurrence of composite renal endpoint

will be formally tested hierarchically in this order at the 0.270% two-sided significance level. If the test for KCCQ produces a non-significant result, the testing of the composite renal endpoint will be performed in an explorative manner only.

Furthermore, the individual components of the primary endpoint (CV deaths and total HF events) will be tested at the 0.270% two-sided significance level outside of the alpha-preserving procedure for the primary and other secondary efficacy endpoints (KCCQ, composite renal).

If the study is not stopped early for success: a group sequential design with a single interim analysis when 2/3 of the information is available with a stopping rule of two-sided $p < 0.00270$ would require a small adjustment to the alpha level at the final analysis to maintain the overall significance level at 5%. For an information fraction of 2/3, the adjusted alpha level of 4.967% applies. If the study is not stopped early for success a p-value of $p<0.04967$ is therefore required at the final analysis to achieve formal statistical significance.

If the primary hypothesis is rejected, the secondary endpoints of:

- Change from baseline to Month 6, 9 and 12 in TSS from KCCQ
- Time to first occurrence of composite renal endpoint

will be formally tested hierarchically in this order at the 4.967% two-sided significance level. If the primary hypothesis is not rejected, these tests will be performed in an explorative manner only; similarly, if the test for KCCQ produces a non-significant result, the testing of the composite renal endpoint will be performed in an explorative manner only.

Furthermore, if the primary hypothesis is rejected then the individual components of the primary endpoint (CV deaths and total HF events) will also be tested at the 4.967% two-sided significance level outside of the alpha-preserving procedure for the primary and other secondary efficacy endpoints (KCCQ, composite renal).

Regardless of whether the study is stopped early for success: as a hard endpoint and objective indicator of benefit-risk, time to ACM will be tested at a two-sided significance level of 5%, after the rejection of the primary hypothesis. Testing of time to ACM will thus be done outside of the alpha-preserving procedure for the primary and other secondary efficacy variables (KCCQ, composite renal).

5. Analysis Sets

5.1 Assignment of Analysis Sets

Final decisions regarding the assignment of subjects to analysis sets will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to analysis set(s) (see Section 4.6).

For purposes of analysis, the following populations are defined:

Population	**Description**
Enrolled	All participants who sign the informed consent form (ICF)

Population	Description
Randomly assigned to study intervention	All participants randomly assigned to study intervention
Safety analysis set (SAF)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Full analysis set (FAS)	All randomized participants. Participants will be analyzed according to the intervention they were randomized to. Only potential reason for exclusion would be a clearly erroneously randomization, or major good clinical practice (GCP) violations, for example, a suspicion of fraud.
Pharmacokinetic analysis set (PKS)	All finerenone-treated subjects (with the exception of subjects excluded on the grounds of critical GCP violations) with at least 1 valid finerenone plasma concentration and without validity findings which would interfere with the evaluation of the pharmacokinetic (PK) data.

6. Statistical Methodology

6.1 Population Characteristics

Population characteristic analyses, except for subject disposition, will be performed for the FAS, if not stated otherwise.

6.1.1 Disposition

The number of subjects enrolled, randomized and valid for the FAS and SAF will be summarized overall and by treatment group, country/region and investigator. The number of subjects discontinuing each epoch, together with the primary reason for discontinuation will be presented by treatment group (post-randomization epochs only) and overall in separate tables. In addition, the number of subjects with important deviations will be presented overall, by investigator and country/region for each treatment group, and in total. The frequencies of each important deviation and validity finding will be presented by treatment group and in total.

6.1.2 Demography and Other Baseline Characteristics

Demography includes age, sex, race, ethnicity, pooled region, body weight, body height, BMI, hip and waist circumference, smoking history (never, former, current smoker) and alcohol consumption. Other baseline characteristics include baseline left ventricle ejection fraction, NYHA Class (II, III, IV), time since index HHF (very recent (≤ 7 days from randomization), recent (>7 days - ≤ 3 months), >3 - ≤ 6 months, >6 - ≤ 9 months, >9 - ≤ 12 months, >12 months - ≤ 2 years, >2 years, no index), serum potassium, categories for serum potassium (≤4.5 mmol and >4.5 mmol), eGFR (calculated by CKD-EPI formula, Japanese formula adjustment made for subjects recruited in Japan), category for eGFR (<=60 vs <60 ml/min/1.73m2), serum creatinine, values for vital signs parameters (i.e. SBP, diastolic blood pressure [DBP] and heart rate), baseline BMI (<18.5, 18.5 to <25, ≥25 to 30, ≥30 to <35, >=35 kg/m2) and additional subgroup categories as described in Section 4.5.4.

All demographic data and baseline characteristics will be tabulated by treatment group and overall. The demographic and other baseline characteristics table will also be presented, separated by each level of the stratification factors.

The non-stratified demographic and other baseline characteristics table will be repeated for the SAF if ≥5% of randomized patients do not take at least one dose of study intervention (i.e. are in the FAS but not the SAF).

As stated in Section 4.2, demographics and other baseline characteristics will also be presented separately for subjects discontinuing the study and for subjects discontinuing study treatment.

6.1.3 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be presented for each MedDRA Primary System Organ Class (SOC) and Preferred Term (PT) by treatment group and overall in a summary table. Additional medical history terms by the following Project-specific Bayer MedDRA Queries (PBMQs), Bayer MedDRA Labeling Groupings (MLGs) or selected PTs will also be presented:

- Hyperlipidemia (MLG)
- Hypertension (MLG)
- Diabetes mellitus
- Atrial fibrillation/flutter (PBMQ)
- Ischemic Stroke/Transitory Ischemic Attack (TIA) (PBMQ)
- Myocardial Infarction (PT)
- Coronary Artery Disease (PT)
- Peripheral Artery Disease (PT)
- Cardiac Failure (MLG)
- Coronary Artery Bypass Graft (CABG) (PBMQ)
- Chronic Obstructive Pulmonary Disease (COPD)
- Percutaneous coronary intervention (PCI) (PBMQ)

The medical history tables will be repeated for SAF.

6.1.4 Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). The number of subjects who took at least one concomitant medication, the number of subjects who took at least one medication that started before administration of study drug and the number of subjects who took at least one concomitant medication that started after start of study drug and the number of subjects who took at least one medication ongoing at baseline (i.e. starting before or on the day of randomization and ending at least one day after the day of randomization) drug will be presented by treatment group and overall using anatomical therapeutic chemical (ATC) classes and subclasses.

These tables will be repeated summarizing the number of subjects with medications in the Standard or Bayer drug groups of interest:

- ACEIs and ARBs
- Angiotensin receptor neprilysin inhibitors (ARNIs)
- Beta-blockers
- Loop diuretics
- Thiazide diuretics
- Digoxin
- Nitrates
- Potassium supplements
- Potassium lowering agents (including binders)
- Alpha blocking agents
- Calcium channel blockers
- Centrally acting antihypertensives
- Strong, unclassified, moderate, weak CYP3A4 inhibitors and CYP3A4 inducers
- Aspirin
- Statins
- History of prior MRA use (yes, no)
- Breast Cancer Resistance Protein (BCRP) substrates
- Organic anion transporting polypeptides (OATP) substrates

Anti-diabetic drugs

- Insulin and analogues
- SGLT-2 inhibitors
- Other anti-diabetic drugs (Dipeptidyl Peptidase 4 inhibitors or Glucagon-like peptide-1 agonists or Biguanides or Sulfonylureas or Alpha glucosidase inhibitors or Metiglinides or Thiazolidinediones.)

A subject will be counted only once within each ATC class / subclass, Standard or Bayer drug group, respectively.

A listing will be provided including all medications classified as a strong, unclassified, moderate, or weak CYP3A4 inhibitor according to the Bayer drug groupings together with the respective classification information.

For potassium lowering agents, ACEIs, ARBs and diuretics, shift tables for changes of use for baseline vs. any time on treatment will be provided.

The number of subjects with MRA use during follow-up will be given by substance, the mean daily dose will also be provided for subjects taking eplerenone, spironolactone or potassium canrenoate.

6.1.5 Treatment Duration, Extent of Exposure and Compliance

The analyses described in this section will be repeated for the SAF if ≥5% of randomized patients do not take at least one dose of study intervention (i.e. are in the FAS but not the SAF). All tables and figures regarding treatment duration, extent of exposure and compliance will be presented by treatment group and overall (unless otherwise stated).

Treatment duration, defined as time from start of study drug to permanent stop of study drug (in months), will be summarized using descriptive statistics by treatment group and overall. In addition, treatment duration will be categorized to ≤ 1 month, 1 – 3 months, >3 – 6 months, >6 – 12 months, and then further six-monthly intervals, and presented with the corresponding number and percentage of subjects. Cumulative treatment duration will be categorized to at least one dose, at least 1 month, at least 3 months, then further 3 monthly intervals. Cumulative treatment exposure over the study in person-years will be given by treatment group. A table will be presented with the absolute and relative frequencies of subjects still on study medication at each visit. Kaplan-Meier plots for "Time to end of study treatment" will be provided, as also described in Section 4.2.

The above analyses will be repeated for study duration, from the day of randomization to the EoS visit.

The extent of exposure to study drug (total amount of intake in grams) and the average daily dose in mg during treatment will be summarized using descriptive statistics by treatment group.

The overall titration status, regardless of actual or sham up-titration, will be summarized with absolute and relative frequencies per treatment group, differentiated by patients starting on 10 mg or 20 mg. In addition, the number of patients with study drug down-titrated or temporarily interrupted (dose recorded as 0 mg) as well as associated reason will be summarized with absolute and relative frequencies per treatment group.

The number and percentage of subjects on each dose level (blinded) and dose (actual) will be summarized by visit and treatment group.

The overall compliance (as a percentage) will be calculated as follows:

100 * Number of tablets taken / Number of planned tablets.

The number of planned tablets will be calculated as follows:

(Days from randomization to last intake of study drug + 1) * Number of planned tablets per day.

For subjects who withdraw prematurely from the study drug, compliance will be calculated up to the time of last dose.

The overall compliance will be summarized descriptively by treatment group and overall. In addition, percentage compliance will be categorized into three groups, less than 80%, 80 to 120% and greater than 120%, and the categories will be summarized by treatment group and overall.

6.2 Efficacy

6.2.1 Analysis of Primary Efficacy Variable

6.2.1.1 Primary Efficacy Variable: Primary Analysis

The primary endpoint is the composite of CV death and total (first and recurrent) HF events (HHF or urgent HF visit) in HF patients. The primary analysis of this endpoint will be performed in the FAS using the planned treatment group, in line with the ITT principle.

Participants without an event of the primary composite endpoint at the time of analysis will be censored at the date of their last contact or date of non-CV death.

The primary analysis of the primary endpoint of the composite will be based on a stratified Andersen-Gill model (Andersen, 1982) including treatment group as fixed effect and including pooled region and baseline LVEF (<60%, ≥60%) as stratification factors. Robust standard errors (sandwich estimator) will be used to account for correlations of event times within a participant. As shown by Lin et al. 2000, the Andersen-Gill model with robust standard errors can be interpreted as a proportional rates model. After the authors of the paper, the model is also referred to as Lin, Wei, Yang and Ying (LWYY) model. Let θ be the RR for the finerenone versus placebo group. In order to evaluate whether finerenone is superior to placebo in reducing the rate of the composite event of CV death and total HF events the following null hypothesis will be tested using the model above (see Section 4.7 for details regarding the nominal significance level):

$$H_0: \theta = 1 \text{ versus } H_1: \theta \neq 1,$$

where a $\theta < 1$ represents a treatment benefit of finerenone over placebo.

A point estimate of the RR together with a 95% CI will be presented, as well as a plot of the mean cumulative function by treatment group.

In terms of the addendum to International Council for Harmonisation (ICH) E9 (ICH 2019), the five attributes of the primary estimand are as follows:

a. Population: as described by inclusion/exclusion criteria given in Section 5 of the protocol

b. Variable: Number of unfavorable events including CV death and total (first and recurrent) hospitalization of heart failure

c. Treatment condition: Finerenone vs. placebo

d. Intercurrent events: There are three important intercurrent events to consider - Treatment discontinuation, CV death and non-CV death. For treatment discontinuation a treatment policy strategy will be applied, i.e. patients will be followed up for events after discontinuing treatment and events and follow-up time after discontinuation of treatment will be included in the analysis. CV death will be counted as both an outcome event as well as a censoring event, so that a combination of a composite and a while alive strategy is used. It is thus assumed that patients could have had further events for HF, if they had not died. This seems appropriate, as including into the model that no further HF events can occur after death, for example by censoring patients at the end of the study, would induce a bias in favor of a treatment group with more early deaths. Non-CV death is assumed to be a censoring event, since the treatment is not assumed to have an effect on these events and interest lies in the treatment effect on composite events while patients are alive. For this a treatment

policy strategy applies as well, that is events will be followed up and analyzed regardless of whether background medication was changed.

e. Population-level summary: Ratio of exposure-weighted composite event rates between finerenone and placebo. Exposure-weighted refers to patients being weighted according to their follow-up time in determining the rate.

The primary analysis method has been investigated with extensive simulation studies and it has been confirmed that it keeps the alpha level and has good operating characteristics across a range of plausible scenarios. A small adjustment will be made to the nominal significance level and the critical value at the final analysis to take into account the interim analysis (see Section 4.7 for details). No adjustment to the sample size calculation is done for this.

The SAS code below illustrates the program for the Anderson-Gill model:

```
PROC PHREG DATA=primary COVS(aggregate);
MODEL (time_start, time_rec)*status(0)=treat/ties=efron rl;
ID patid;
STRATA {stratum};
RUN;
```

`primary` is the input dataset, `time_start` is the previous event stop time and `time_rec` is the current event stop time, the censoring variable `status` (0 for censored and 1 for event) should take the value 1 if the last event is a CV death and 0 if it is censored for a non-CV death or at the end of study for the given patient; `patid` is the subject ID.

If a subject is hospitalized for HHF and dies for a cardiovascular reason during the hospitalization, this will be considered as a single event for the primary analysis (and as both an HHF as well as a CV death for the component analyses), unless the subject dies more than seven days after the start of the hospitalization. If an additional event occurs after the discharge of the patient from an HHF or the end of an urgent HF visit, it will only be considered to be a separate event for the primary analysis if the start date is at least seven days after the end of the previous event.

A plot of the mean cumulative function of events (Nelson-Aalen estimate) by treatment group will be provided. Non-parametric estimates of unconditional HF event rates over time allowing for death as terminal event will be provided as well (Ghosh and Lin 2000).

6.2.1.2 Primary Efficacy Variable: Supportive Analysis

As part of the primary analysis, separate estimates of treatment effects for the components of the primary endpoint, total HF events and CV death will be obtained. For this analysis, a joint frailty model will be used (Rogers et al. 2016). This model gives a treatment effect on total HF events which is adjusted for a potential treatment effect on CV death. An effect on CV death might otherwise dilute the effect seen on the hospitalizations, i.e. an effective treatment will prevent CV deaths especially in the more severely ill participants, which then potentially realize many hospitalizations. The joint frailty model will be fitted using the method described in the paper by Liu and Huang (2008) where the unknown baseline hazard for CV death and unknown baseline intensity for HF events are approximated by piecewise constant functions.

A gamma frailty distribution will be assumed. As a sensitivity analysis a joint frailty model with constant hazard and intensity functions will be fitted as well. The flexible model can sometimes have convergence issues, should this occur, the estimate of the treatment effect on HF events of the model with the constant baseline functions will be considered to be the main estimate.

For CV death the main treatment effect estimate will be derived from a stratified Cox proportional hazards model for time to CV death and the main p-value from a stratified log-rank test, the estimate from the joint frailty model will be considered supportive.

Note that the study is not powered to show an effect on CV death alone. While this is the case, a sufficient number of deaths are expected so that an excess risk in mortality can be excluded. Under the assumptions of the sample size determination, approximately 535 CV deaths and approximately 775 all-cause deaths are expected to occur in the study. Even though no formal statistical tests for exclusion of an increased risk will be performed, these expected event counts would result in a relatively high power to exclude increased hazard ratios (HRs) on ACM. Table 6–1 provides the respective power values to exclude HRs above 1.15 and 1.25 under different assumed values for the true HR on CV death and assuming no treatment effect on non-CV deaths (HR_{NonCVD}=1.0). Similar to the primary endpoint, a treatment policy strategy is used for treatment discontinuation. With exclusion of a certain HR value it is meant that the upper limit of a 95% CI is below the value.

Table 6–1: Power to exclude increased HR on ACM under different assumed treatment effects on CV death

True HR_{CVD}	Exclude HR_{ACM}>1.15	Exclude HR_{ACM}>1.25
0.8	94%	>99%
0.9	78%	97%
1.0	52%	88%

As supportive analysis, stratified Cox proportional hazard regression analyses will be performed for the following endpoints, with Kaplan-Meier plots being provided:

- Time to first composite of HF event or CV death
- Time to first HF event
- Time to first HHF
- Time to first urgent HF visit
- Time to first composite of HHF or CV death

An additional analysis of the primary endpoint will exclude urgent HF visits and consider only CV deaths and HHFs as events. Additionally, joint frailty models will be used to estimate effects of time to recurrent HHFs and time to recurrent urgent HF events, adjusted for a potential effect on CV death.

As a sensitivity analysis, the number of primary composite events will also be analyzed using a negative binomial regression model including stratification factors and treatment group as covariates and log follow-up time as an offset parameter.

A total-time approach considering times from randomization to the onset of first, second, third composite event using a Wei, Lin, and Weissfeld, 1989 model will be applied. This model enables analysis of the cumulative effect on the primary endpoint from randomization (i.e. the effect on second event includes the effect on the first, and the effect on third event includes the effects on the first and second). The corresponding individual HRs with 95% CIs

comparing treatment groups on the first, second, and third event will be presented. In addition, a conditional gap-time model according to Prentice, Williams and Peterson (1981) will be applied to obtain HR estimates with 95% CIs for the time from first to second and from second to third event (note that this gives a non-randomized comparison). Both models will employ robust standard errors and include the stratification factors and treatment group as fixed effects.

An "on-treatment" analysis will be performed, including only events occurring up to 30 days after treatment discontinuation and within 5 months after the last visit with complete information on all components of the composite primary endpoint. A 5-month time window is used as visits are 4-monthly and in order to allow for late attendance by an additional 1 month. This analysis will be performed in the SAF instead of the FAS.

To examine whether the treatment effect seems to be stable over time, a time-treatment interaction will be included in the primary analysis model.

The primary analysis for the primary endpoint will also be repeated for the "Total HF events and ACM" endpoint.

In addition, the primary analysis will also be repeated where patients are included with only up to a maximum of 4 composite events, to examine the impact of patients with a large number of events.

A further sensitivity analysis will be performed including all HF events and CV deaths regardless of when they occur in relation to a patient's previous HF event (i.e. ignoring the 7-day rules as described in Section 6.2.1.1).

Events that could potentially fulfill the criteria for primary efficacy variables during the study will be evaluated by the CEC. Definitions of individual endpoints (e.g. CV death) will be provided in the Endpoint Manual.

6.2.2 Analysis of Secondary Efficacy Variables

6.2.2.1 Secondary Efficacy Variables: Primary Analysis

Secondary efficacy variables are the following:

- Change from baseline to Month 6, 9 and 12 in TSS of the KCCQ
- Time to first occurrence of composite renal endpoint: sustained decrease in eGFR ≥40% relative to baseline over at least 4 weeks, or sustained eGFR decline <15ml/min/1.73m^2 or initiation of dialysis or renal transplantation
- Time to ACM

See Section 4.7 for details regarding the testing hierarchy for secondary endpoints and nominal significance levels.

The absolute change from baseline including measurements up to month 12 of the KCCQ TSS will be analyzed by a repeated measures mixed model including the factors treatment group, baseline, visit, baseline-by-visit interaction, and factors for the stratification levels. Differences between the finerenone and the placebo treatment groups will be calculated with two-sided 95% CIs. The comparison assumes a common treatment effect across month 6, 9 and 12 and will be considered primary. This analysis will investigate the effect on the KCCQ

TSS while patients are alive and irrespective of any permanent treatment discontinuation. This means that all observed values will be included in the analysis.

The primary analysis of the secondary time-to-event variables (i.e. composite renal endpoint and ACM) will be done with a stratified log-rank test for testing and a stratified Cox proportional hazards model for obtaining a point estimate with 95% CIs. The Cox proportional hazards model will be stratified according to the stratification factors and include treatment group as fixed effect.

Only central laboratory measurements before initiation of dialysis or renal transplantation will be considered for the definition of the individual eGFR-based components of the renal endpoint. At the up-titration, restart and safety check visits, only a local laboratory measurement is obtained. These values will be checked for a potential eGFR event and, in case of decline, the investigators will be advised to retest eGFR centrally in an unscheduled visit; determination of an eGFR event will then be based on this value. Events will be counted from the day of randomization until the EoS visit. If an initial decrease in eGFR occurs on the EoS visit, there will be another confirmatory measurement taken at least 4 weeks later to confirm the initial decrease. The individual components "Sustained decrease of eGFR $\geq$ 40% from baseline over at least 4 weeks" as well as "Sustained eGFR decline <15ml/min/1.73m^2" will be programmatically derived. Only in case the eGFR decrease was confirmed by at least one additional eGFR measurement taken at least 4 weeks later, it will be considered as a sustained decrease and counted for the renal endpoint. The date used for the analysis will be the date of the initial sample exceeding the threshold. In case there was no confirmatory assessment, events will only be counted for the renal endpoint when the patient died after the initial decrease or the patient went on renal replacement therapy such as dialysis or transplantation. If there is an intermediate measurement that does not confirm the initial decrease, the event will not be counted for the renal endpoint.

The other two components of the renal endpoint, i.e. initiation of dialysis or renal transplantation, will be adjudicated. To account for events of initiation of dialysis after the last eGFR is recorded at a clinic visit, such events will be included in the efficacy analysis of the composite renal endpoint if they occur in the period up to one day before the next planned clinic visit. Censoring will be applied at next protocol scheduled visit plus 1 month. For a death in this period, the date of death will be used as the censoring date. Randomized subjects without an event of the composite renal endpoint at the time of analysis will be censored at the date of their last visit when complete information on all components of the composite renal endpoint is available, up to and including the EoS visit (should this visit satisfy this rule), or date of death using a time window next protocol scheduled visit plus 1 month as above if a subsequent clinic visit had been planned.

6.2.2.2 Secondary Efficacy Variables: Supportive Analysis

The additional analyses of the secondary time-to-first event endpoints will include Kaplan-Meier plots and an "on-treatment analysis". The proportional hazards assumption will also be investigated by including a time-treatment interaction into the model and plotting smoothed Schoenfeld residuals. For the renal endpoint, a time-to-first event analysis will be done separately for each of the components.

A supportive analysis of the KCCQ TSS will apply a worst-case imputation for death which means that if a patient dies, a worst score of 0 for the TSS will be imputed for all subsequent visits after the patient's death. Treatment effects at month 6, 9 and 12 will also be investigated individually by adding a treatment-by-visit interaction into the model.

A responder analysis for the KCCQ TSS will also be performed, defining patients with an increase of ≥5 points from baseline to Month 9 (or, for those with a baseline score of >95, a score of >95 at Month 9) as a responder. All observed values will be included irrespective of any permanent treatment discontinuation. In case of missing data, a patient's last available post-baseline score prior to Month 9 will be used unless the patient died in which case they will be imputed as a non-responder. Responder status will be analysed using a logistic regression model including treatment, baseline TSS and stratification factors as covariates; the odds ratio and associated 95% CI will be reported. This analysis will be repeated for cut-offs of ≥10 points increase from baseline to Month 9 (or maintaining a score of >90 from baseline to Month 9) and ≥20 points increase (or maintaining a score of >80). These cut-offs correspond to small (≥5), moderate (≥10) and large (≥20) clinically meaningful improvements (Spertus et al, 2005). A further analysis will define those responders who do not experience a ≥5 points decrease from baseline (or, for those with a baseline score of <5, a score of ≥5 at Month 9). This is equivalent to not experiencing a small deterioration. The number and percentage of patients who are responders or non-responders per each of the above criteria will be presented at Months 6, 9 and 12. This will include a breakdown of the criteria met for response (e.g. increase from baseline of ≥5, >95 at baseline and post-baseline visit) or non-response (e.g. change from baseline of <5, >95 at baseline and ≤95 at post-baseline visit, missing score at post-baseline visit).

6.2.3 Analysis of Further Exploratory Efficacy Variables

Other exploratory efficacy variables will be as follows:

- Time to first CV hospitalization
- Time to first all-cause hospitalization
- Total number of CV hospitalizations
- Total number of all-cause hospitalizations
- Time to first occurrence of the following composite endpoint: CV death or non-fatal CV event (i.e. non-fatal myocardial infarction, non-fatal stroke, or HHF)
- Change from baseline in eGFR
- Days alive and out of hospital (DAOH)
- Time to new onset of atrial fibrillation
- Change in health-related quality of life summary scores from baseline measured by KCCQ and EuroQol Group 5-dimension 5-level questionnaire (EQ-5D-5L)
- Change from baseline in NYHA class

Exploratory time-to-event variables will be analyzed using the stratified log-rank test and the stratified Cox proportional hazards model. Kaplan-Meier plots will be provided.

The total number of CV hospitalizations will be analyzed using an LWYY model, similarly to the primary efficacy endpoint, and will be summarized descriptively by treatment group together with the annual rate of CV hospitalizations. These summaries and analyses will be repeated for all-cause hospitalizations.

The absolute change from baseline in eGFR at each visit until Visit 10 (Month 24) will be analyzed by a mixed model with the factors treatment group, baseline eGFR, visit, treatment-by-visit interaction, baseline-by-visit interaction, and factors for the stratification levels

(pooled region and LVEF). Differences between the finerenone and placebo treatment groups at each visit will be calculated, and corresponding two-sided 95% CIs will be computed.

Frequency tables will be generated for the number and percentage of patients with a relative decrease in eGFR of ≥25%, ≥30%, ≥40%, ≥50% and ≥57% from baseline. The analysis will be performed for each visit and for any time post-baseline.

For each patient, the annual change in eGFR will be calculated by fitting the patient's eGFR assessments into a linear regression model with time as the independent variable. The derived annual change will be analyzed using an analysis of covariance (ANCOVA) model including baseline eGFR, treatment group and stratification factors as fixed effects.

DAOH will be summarized descriptively by treatment group; the percentage of DAOH with respect to total potential follow-up time as well as the number of days in hospital will also be provided. These analyses will be performed overall and separately by the stratification factors (pooled region and LVEF).

DAOH will be analyzed by an ANCOVA model including potential follow-up time, treatment group, and stratification factors as fixed effects. Potential follow-up time is defined as the time from randomization up to end of study or lost to follow-up or withdrawal date, in case the patient did not complete the study.

DAOH will be analyzed once considering the total potential follow-up time and once considering only the first year of follow-up.

For the KCCQ, 3 further summary scores (physical limitation score [PLS], clinical summary score [CSS] and overall summary score [OSS]) will be derived. For the KCCQ PLS, CSS and OSS, the absolute change from baseline including measurements up to month 12 of the KCCQ TSS will be analyzed by a repeated measures mixed model including the factors treatment group, baseline, visit, baseline-by-visit interaction, and factors for the stratification levels. Differences between the finerenone and the placebo treatment groups will be calculated with two-sided 95% CIs. In addition, descriptive statistics will be presented by visit and treatment group: number of observations, number of missing values, minimum, first quartile, mean, standard deviation, median, third quartile, and maximum, including the changes from baseline. The analyses for TSS are described in Section 6.2.2.

For the EQ-5D-5L, summary scores will be calculated from the 5 dimensions according to the scoring instructions from UK and the US (refer to the EQ-5D-5L User Guide (EuroQoL Group 2013) and to the EQ-5D Value Sets (Szende et al. 2007). The values and the changes from baseline of the summary scores and the EuroQol Group visual analogue scale (EQ VAS) will be summarized by treatment group and visit using the same descriptive statistics as for KCCQ.

Change from baseline in NYHA class will be summarized descriptive using shift tables, presented by visit and any time post-baseline.

6.2.3.1 Patient Global Impression of Change (PGIC) and Severity (PGIS)

A sub-population of 1200 participants will be asked the following questions at baseline (PGIS only) and at Visit 4 (Month 6), Visit 5 (Month 9) and Visit 6 (Month 12):

- PGIC: the participant is asked to assess the degree of change in their HF symptoms compared to the start of the treatment using the following response options: much better, better, a little better, the same, a little worse, worse or much worse

- PGIS: the patient is asked to assess the current severity of their HF symptoms due to HF using the following response options: no symptoms, mild, moderate, severe or very severe

These questions will be used as an anchor to provide an estimate of clinically meaningful change in the KCCQ TSS. Details of the analysis, to be described in a separate SAP, will be conducted on a blinded dataset and reported separately from the CSR.

6.2.4 Outcome Events Reported by the Investigators

Outcome events using the investigator-reported terms will be summarized by treatment group, using tables analogous to those for AEs. Only adjudicated outcome events will be used for the analysis of the primary composite endpoint. Adjudication of the secondary renal endpoint will be restricted to cases of initiation of dialysis or renal transplant. No adjudication will be done for events only included in an exploratory efficacy endpoint (e.g. non-fatal myocardial infarction) and therefore the investigator-reported events will be used in the analysis of those endpoints. An overall summary of all outcome events will be generated by treatment group.

The number of subjects with all outcome events, outcome events from randomization up to 30 days after stop of study medication, post-treatment outcome events occurring more than 30 days after stop of study drug or after the EoS Visit and outcome events by maximum intensity will be summarized by treatment group using MedDRA terms grouped by Primary SOC and PT.

The incidence rate of outcome events per 100 patient-years will also be provided by treatment group using MedDRA terms grouped by Primary SOC and PT. The time under risk for the incidence rates is defined as the time from randomization until the first onset of the event or the last date of contact with the subject in case no such event is recorded.

Outcome events will be listed separately in the section 14.2 tables.

6.3 Pharmacokinetics/pharmacodynamics

6.3.1 Pharmacokinetics

The finerenone plasma concentration versus time data collected at various study visits will be evaluated descriptively, separated by dose and visit. Plots will be prepared of all individual plasma concentrations vs. actual relative study times (time of sample collection after time of study drug administration).

Evaluation of the concentration data will be performed using Population Pharmacokinetic (PK) methods, followed by PK / Pharmacodynamic (PD) analyses. These analyses will be described in a separate Analysis Plan outside of this document and will be reported separately.

6.3.2 Pharmacodynamics

Analysis of the pharmacodynamics parameters (e.g. blood pressure, heart rate, laboratory values) will be described in detail in a separate SAP.

6.4 Safety

All analyses on safety and tolerability data will be performed in SAF.

6.4.1 Adverse Events

AEs will be coded using the latest version of MedDRA available prior to database freeze. A listing will be provided linking the original investigator terms and the coded terms. AEs will also be presented grouped by standardized MedDRA queries (SMQs).

AEs that occurred or worsened after the first dose of study drug and up to 3 days after the last dose of study drug will be considered as treatment-emergent AEs (TEAEs).

An overall summary of all AEs and TEAEs will be generated by treatment group.

The number of subjects with TEAEs, post-treatment AEs occurring more than 3 days after stop of study drug, treatment-emergent serious adverse events (SAEs), treatment-emergent study drug-related AEs, treatment-emergent study drug-related SAEs, TEAEs causing discontinuation of study drug, treatment-emergent non-serious AEs, TEAEs by maximum intensity, drug-related TEAEs by maximum intensity and TEAEs with fatal outcome and will be summarized by treatment group using MedDRA terms grouped by Primary SOC and PT.

The incidence of TEAEs and treatment-emergent SAEs per 100 person-years will also be provided by treatment group using MedDRA terms grouped by Primary System Organ Class and Preferred Term. This analysis will consider the first AE for a subject.

In case of events with different intensity within a subject, the maximum reported intensity will be used. If intensity is missing, the event will be considered as severe. If the same event is reported as both unrelated and related to the study drug within a subject, the event will be considered as related to study drug. If the drug relationship is missing, the event will be considered as being related to the study drug. Deaths and SAEs will be listed separately.

Any AEs/SAEs related to study procedure recorded after signing of informed consent but prior to randomization will be tabulated separately.

6.4.2 Laboratory Parameters

The number of subjects with treatment-emergent (after the first dose of study drug and up to 3 days after last dose of study drug) abnormal laboratory values above or below the normal range will be tabulated by the laboratory parameter and treatment group.

Summary statistics including changes to baseline will be calculated by treatment group and visit for all quantitative laboratory parameters, e.g. for hematology, NT-pro BNP, high sensitive troponin T (hs-TNT), clinical chemistry and urinalysis. Geometric statistics and ratios to baseline will be presented for creatinine and NT-proBNP instead of arithmetic statistics with changes from baseline. For eGFR the relative change will be displayed in addition to the absolute change from baseline.

Summary statistics for serum potassium, eGFR, NT-pro BNP, hs-TNT and serum creatinine will also be repeated by treatment group and visit separately for each level of the stratification factors.

The following special safety parameters will be further assessed by displaying the number of subjects with safety events as described below by treatment group, visit and for any time on treatment (including unscheduled assessments) and up to 3 days after last study drug administration. This will also be performed by stratification factors. The summaries will be performed for the number of subjects with:

- Absolute value of serum potassium >5.0 mmol/L, >5.5 mmol/L, >6.0 mmol/L and >7.0 mmol/L

- Relative decrease from baseline in eGFR of ≥25%, ≥30%, ≥40% and ≥57%, also sustained decrease over 4 weeks
- Absolute value of eGFR < 25 ml/min/1.73m²
- Increase from baseline in serum creatinine >0.3 mg/dL and >0.5 mg/dL.

The percentage of subjects with the respective events (non-stratified) at any time post-baseline (including unscheduled assessments) and within 3 days after last study drug administration will be compared between the finerenone and placebo group by applying separate explorative χ^2 tests with continuity correction. If the expected number of subjects in at least 1 cell of the 2x2 contingency table is <5 (Agresti 2005), Fisher's exact test will be applied instead of the χ^2 test. Estimates and two-sided 95% CIs will be provided for each treatment group and the treatment differences. Clopper-Pearson CIs will be calculated for each treatment group, while for treatment differences the exact unconditional confidence limits will be calculated.

6.4.3 Other Additional Safety Variables

6.4.3.1 Vital Signs

At the corresponding visits, 2 BP and 1 pulse measurements of vital signs parameters will be taken. Averages of non-missing values of these two BP measurements will be calculated and used for the statistical analysis. If only one of the planned measurements is available, this value will be used.

Vital signs values will be summarized by treatment group and visit using descriptive statistics including absolute changes from baseline. The analysis will be repeated for SBP stratified by baseline SBP ≥90 to <130 mmHg, 130 to <160 mmHg and ≥160 mmHg.

6.4.3.2 Weight and BMI

The values and the changes from baseline will be summarized by treatment group and visit using descriptive statistics for weight and BMI.

6.4.3.3 Further Safety Variables

Further safety variables listed in section 9.4.2 of the protocol not covered in the above sections are the presence or absence of events associated with hyperkalemia and renal failure. These will be summarized by treatment group using frequency counts.

6.5 COVID-19 and Related Issues

It is expected that the COVID-19 pandemic will have some impact on this trial. Every effort, including but not limited to the following, will be made to capture the effect of COVID-19:

- Listing of all patients affected by COVID-19 related study disruption: site, comment with all details why individual's study participation was altered
- Number of patients affected, number of skipped visits, number and type of protocol deviations will be tabulated
- A pre-specified MHTERM for COVID-19 will be included in Medical History
- All adjudicated outcome events will be additionally adjudicated for relationship to COVID-19 (related, possibly related, unrelated, unknown relationship)

The impact of COVID-19 will be monitored on an ongoing basis during the trial. If the impact is large, additional summaries and sensitivity analyses may be defined in a SAP amendment.

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8. Appendix

8.1 The Kansas City Cardiomyopathy Questionnaire Scoring Instructions

There are 10 summary scores within the KCCQ, which are calculated as follows:

1. Physical Limitation

- Code responses to each of Questions 1a-f as follows:

  Extremely limited = 1
  Quite a bit limited = 2
  Moderately limited = 3
  Slightly limited = 4
  Not at all limited = 5
  Limited for other reasons or did not do = <*missing value*>

- If at least three of Questions 1a-f are not

  missing, then compute

  Physical Limitation Score = 100*[(mean of Questions 1a-f actually answered)

  – 1]/4 *(see footnote at end of this document for explanation of meaning of*

  "actually answered")

2. Symptom Stability

- Code the response to Question 2 as follows:

  Much worse = 1
  Slightly worse = 2
  Not changed = 3
  Slightly better = 4
  Much better = 5
  I've had no symptoms over the last 2 weeks = 3

- If Question 2 is not missing, then compute

  Stability Score = 100*[(Question 2) – 1]/4

3. Symptom Frequency

- Code responses to Questions 3, 5, 7 and 9 as follows:

  <u>Question 3</u>
  Every morning = 1
  3 or more times a week but not every day = 2
  1-2 times a week = 3

Less than once a week = 4
Never over the past 2 weeks = 5

Questions 5 and 7
All of the time = 1
Several times a day = 2
At least once a day = 3
3 or more times a week but not every day = 4
1-2 times a week = 5
Less than once a week = 6
Never over the past 2 weeks = 7

Question 9
Every night = 1
3 or more times a week but not every day = 2
1-2 times a week = 3
Less than once a week = 4
Never over the past 2 weeks = 5

- If at least two of Questions 3, 5, 7 and 9 are not missing, then compute:

  S3 = [(Question 3) – 1]/4
  S5 = [(Question 5) – 1]/6
  S7 = [(Question 7) – 1]/6
  S9 = [(Question 9) – 1]/4

  Symptom Frequency Score = 100*(mean of S3, S5, S7 and S9)

4. Symptom Burden

- Code responses to each of Questions 4, 6 and 8 as follows:

  Extremely bothersome = 1
  Quite a bit bothersome = 2
  Moderately bothersome = 3
  Slightly bothersome = 4
  Not at all bothersome = 5
  I've had no swelling/fatigue/shortness of breath = 5

- If at least one of Questions 4, 6 and 8 is not missing, then compute

  Symptom Burden Score = 100*[(mean of Questions 4, 6 and 8 actually answered) – 1]/4

5. Total Symptom Score

= mean of the following available summary scores: Symptom Frequency Score

Symptom Burden Score

6. Self-Efficacy

- Code responses to Questions 10 and 11 as follows:

Question 10
Not at all sure = 1
Not very sure = 2
Somewhat sure = 3
Mostly sure = 4
Completely sure = 5

Question 11
Do not understand at all = 1
Do not understand very well = 2
Somewhat understand = 3
Mostly understand = 4
Completely understand = 5

- If at least one of Questions 10 and 11 is not missing, then compute Self-Efficacy Score = 100*[(mean of Questions 10 and 11 actually answered) – 1]/4

7. Quality of Life

- Code responses to Questions 12, 13 and 14 as follows:

Question 12
It has extremely limited my enjoyment of life = 1
It has limited my enjoyment of life quite a bit = 2
It has moderately limited my enjoyment of life = 3
It has slightly limited my enjoyment of life = 4
It has not limited my enjoyment of life at all = 5

Question 13
Not at all satisfied = 1
Mostly dissatisfied = 2
Somewhat satisfied = 3
Mostly satisfied = 4
Completely satisfied = 5

Question 14
I felt that way all of the time = 1
I felt that way most of the time = 2
I occasionally felt that way = 3
I rarely felt that way = 4
I never felt that way = 5

- If at least one of Questions 12, 13 and 14 is not missing, then compute

Quality of Life Score = 100*[(mean of Questions 12, 13 and 14 actually answered) – 1]/4

8. Social Limitation

- Code responses to each of Questions 15a-d as follows:

Severely limited = 1
Limited quite a bit = 2
Moderately limited = 3
Slightly limited = 4
Did not limit at all = 5
Does not apply or did not do for other reasons = <*missing value*>

- If at least two of Questions 15a-d are not missing, then compute

Social Limitation Score = 100*[(mean of Questions 15a-d actually answered) – 1]/4

9. Overall Summary Score

= mean of the following available summary scores: Physical Limitation Score
Total Symptom Score Quality of Life Score Social Limitation Score

10. Clinical Summary Score

= mean of the following available summary scores: Physical Limitation Score
Total Symptom Score

Note: references to "**means of questions actually answered**" imply the following.

f If there are *n* questions in a scale, and the subject must answer *m* to score the scale, but the subject answers only *n-i*, where *n-i* >= *m*, calculate the **mean of those questions** as
(sum of the responses to those *n-i* questions) / (*n-i*) **not**
(sum of the responses to those *n-i* questions) / *n*

Title Page

A multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of finerenone on morbidity and mortality in participants with heart failure (NYHA II-IV) and left ventricular ejection fraction ⩾ 40% (LVEF ⩾ 40%)

FINEARTS-HF: **FIN**erenone trial to investigate **E**fficacy and s**A**fety superio**R** to placebo in pa**T**ient**S** with **H**eart **F**ailure

Bayer study drug	Finerenone / BAY 94-8862		
Study purpose:	Efficacy and safety		
Clinical study phase:	III	**Date:**	20 JUN 2024
Study No.:	20103	**Version:**	3.0
Authors:	PPD PPD PPD PPD PPD PPD PPD PPD PPD		

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Abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
ACM	All-cause mortality
AE	Adverse event
ANCOVA	Analysis of covariance
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
ATC	Anatomical therapeutic chemical
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass graft
CEC	Clinical event committee
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLIPS	Clinical Pharmacology Standards
COPD	Chronic obstructive pulmonary disease
CSR	Clinical study report
CSS	Clinical Summary Score
CoV	Coefficient of Variation
CV	Cardiovascular
CYP3A4	Cytochrome P450 isoenzyme 3A4
DAOH	Days alive and out of hospital
DBP	Diastolic blood pressure
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EoS	End of study
EQ VAS	EuroQol Group visual analogue scale
EQ-5D-5L	EuroQol Group 5-dimension, 5-level questionnaire
FAS	Full analysis set
GCP	Good clinical practice
HF	Heart failure
HHF	Hospitalization for heart failure
HR	Hazard ratio
hs-TNT	High sensitive troponin T
ICF	Informed consent form
ICH	International Council for Harmonisation
ITT	Intention-to-treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
LLOQ	Lower limit of quantification
LVEF	Left ventricular ejection fraction
LWYY	Lin, Wei, Yang and Ying
MedDRA	Medical Dictionary for Regulatory Activities
MLG	MedDRA labeling groupings
MR	Mineralocorticoid receptor
MRA	Mineralocorticoid receptor antagonist
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
OATP	Organic anion transporting polypeptides
OD	Once daily
OSS	Overall Summary Score
PBMQ	Project-specific Bayer MedDRA Queries
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic

PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic
PKS	Pharmacokinetic analysis set
PLS	Physical Limitation Score
PT	Preferred term
PWP	Prentice, Williams and Peterson
RR	Rate ratio
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SGLT-2	Sodium-glucose transport proteins-2
SMQs	Standardized MedDRA queries
SOC	System organ class
SPA	Special protocol assessment
TEAE	Treatment-emergent adverse event
TIA	Transitory ischemic attack
TLFs	Tables, Listings and Figures
TSS	Total Symptom Score
UACR	Urinary albumin-to-creatinine ratio
ULOQ	Upper limit of quantification
WHO-DD	World Health Organization Drug Dictionary
WLW	Wei, Lin and Weissfeld

1. Introduction

This Statistical Analysis Plan (SAP) is based on the following document:

Clinical Study Protocol Amendment 20103 dated 26 OCT 2022

This SAP describes the statistical analysis of the double-blind placebo-controlled study treatment phase. An independent data monitoring committee (DMC) will be involved in the review of data for safety and efficacy as will be described in the DMC Charter. Blinded adjudication of clinical outcomes will be performed by an independent Clinical Event Committee (CEC), as will be described in the CEC Charter.

2. Study Objectives

Please refer to the study protocol for details on finerenone and on heart failure.

Study 20103 will be the first large-scale, long-term outcome study investigating the efficacy and safety of the non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone on morbidity and mortality in participants with heart failure (New York Heart Association [NYHA] class II-IV) and left ventricular ejection fraction ≥40% (LVEF ≥40%), in comparison to placebo and in addition to standard-of-care therapy for congestion and comorbidities. Primary endpoint includes Cardiovascular (CV) death and total (first and recurrent) heart failure (HF) events (hospitalizations for heart failure [HHF] or urgent HF visits) in HF patients (NYHA class II–IV) and LVEF ≥40%. Secondary endpoints will include: total HF events; improvement in NYHA class from baseline to Month 12; change from baseline to Month 6, 9 and 12 in total symptom score (TSS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ); time to first occurrence of composite renal endpoint: sustained decrease in estimated glomerular filtration rate (eGFR) ≥50% relative to baseline over at least 4 weeks, or sustained eGFR decline <15ml/min/1.73m^2 or initiation of dialysis or renal transplantation; time to all-cause mortality (ACM); and the safety and tolerability of finerenone.

The Phase III program with finerenone in patients with type 2 diabetes and clinical diagnosis of chronic kidney disease (CKD) encompasses 2 placebo-controlled, large-scale, long-term outcome trials: FIDELIO-DKD, the first large-scale, long-term outcome trial that examined whether finerenone can slow the progression of kidney disease and FIGARO-DKD which is examining the effects of finerenone on CV outcomes. The pooled analysis of two complementary trials (FIDELITY-DKD) comprising 13026 patients with a broad spectrum of CKD and type 2 diabetes provides robust evidence of both cardiovascular and kidney protection with finerenone vs. placebo. Across the FIDELITY-DKD population, the relative risk reduction was 14% for the composite cardiovascular outcome of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure and 23% for the composite kidney outcome of kidney failure, a sustained ≥57% decrease in estimated glomerular filtration rate from baseline over ≥4 weeks, or renal death. While MRAs are indicated for the treatment of patients with chronic symptomatic heart failure with reduced ejection fraction, such patients were excluded from the FIDELIO-DKD and FIGARO-DKD studies. The FIDELITY-DKD analysis provides evidence that finerenone use in patients with CKD and type 2 diabetes, a population at high risk of developing heart failure, significantly reduces the risk of developing HHF. In the FIDELITY-DKD analysis, reduction in HHF was

the main driver of the cardiovascular benefit with finerenone, with a relative risk reduction of 22% vs. placebo (p= 0.0030), in a population that excluded patients with chronic symptomatic heart failure with reduced ejection fraction at the run-in visit.An inappropriate release of aldosterone contributes to target organ damage found in HF, myocardial infarction, chronic renal failure, and hypertension. The extensive expression of the mineralocorticoid receptor (MR) in the CV and renal systems, including the heart, endothelial cells, vascular smooth muscle cells, and kidney mesangial cells, provides further evidence for the role of aldosterone in CV and renal injury.

Blockade of the action of aldosterone and potentially other MR ligands such as cortisol has been demonstrated to be of benefit in HF (Pitt et al. 1999, Zannad et al. 2010). Results from a short-term Phase IIb study (ARTS-HF Study 14564) suggest that treatment with finerenone in addition to standard therapy for HF with LVEF ≤40% improves mortality and CV morbidity outcomes; however, long-term outcome conclusive studies examining whether MRAs can prevent CV events are still lacking in this patient population. Study 20103 will be the first study to address these questions in the HF with LVEF ≥40% population.

The **primary objective** of this study is to:

- Demonstrate the superiority of finerenone to placebo in reducing the rate of CV death and total (first and recurrent) HF events (HHF or urgent HF visit) in HF patients (NYHA II–IV) and LVEF ≥40%.

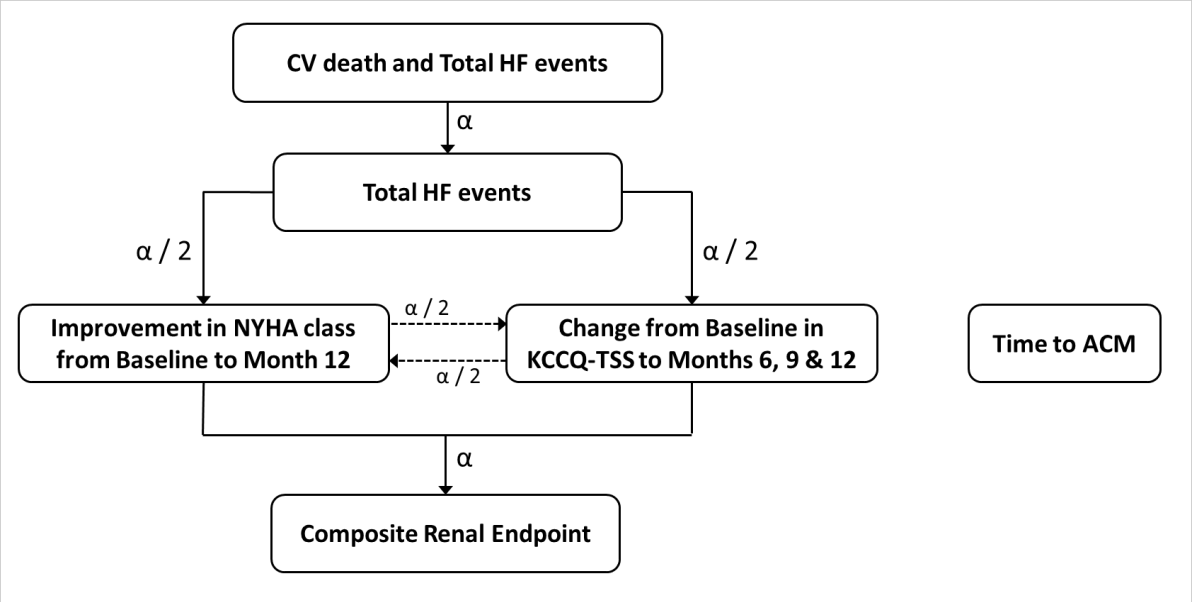
The **secondary objectives** of this study, irrespective of the testing procedure as defined in section 4.7, are to:

- Determine the superiority of finerenone to placebo with regard to each of the following:
    - Reducing the rate of total (first and recurrent) HF events
    - Improvement in NYHA class from Baseline to Month 12
    - Change from baseline to Month 6, 9 and 12 in TSS from KCCQ
    - Time to first occurrence of composite renal endpoint:

      sustained decrease in eGFR ≥50% relative to baseline over at least 4 weeks, or sustained eGFR decline <15ml/min/1.73m^2 or initiation of dialysis or renal transplantation
    - Time to ACM
- Assess the safety and tolerability of finerenone

The testing procedure for the primary and secondary endpoints is presented in Figure 2-1, and described in detail in Section 4.7.

Figure 2-1: Testing procedure for primary and secondary endpoints



In terms of the addendum to International Council for Harmonisation (ICH) E9 (ICH 2019), the five attributes of the primary estimand to address the primary objective of the study are as follows:

a. Population: as described by inclusion/exclusion criteria given in Section 5 of the protocol

b. Variable: Number of unfavorable events including CV death and total (first and recurrent) heart failure events

c. Treatment condition: Finerenone vs. placebo

d. Intercurrent events: There are three important intercurrent events to consider - Treatment discontinuation, CV death and non-CV death. For treatment discontinuation a treatment policy strategy will be applied, i.e. patients will be followed up for events after discontinuing treatment and events and follow-up time after discontinuation of treatment will be included in the analysis. CV death will be counted as both an outcome event as well as a censoring event, so that a combination of a composite and a while alive strategy is used. It is thus assumed that patients could have had further events for HF, if they had not died. This seems appropriate, as including into the model that no further HF events can occur after death, for example by censoring patients at the end of the study, would induce a bias in favor of a treatment group with more early deaths. Non-CV death is assumed to be a censoring event, since the treatment is not assumed to have an effect on these events and interest lies in the treatment effect on composite events while patients are alive.

e. Population-level summary: Ratio of exposure-weighted composite event rates between finerenone and placebo. Exposure-weighted refers to patients being weighted according to their follow-up time in determining the rate.

A pooled analysis of study 20103 with studies FIDELIO-DKD and FIGARO-DKD will be pre-specified and analyses will be described in a separate SAP. Additional analyses for specific scientific questions outside of the scope of the clinical study report (CSR) will be pre-specified in a separate scientific SAP.

3. Study Design

Study 20103 is a randomized, double-blind, parallel-group, placebo-controlled, multicenter, event-driven Phase III study with independently adjudicated clinical outcome assessments. This study will be conducted in patients with HF and LVEF ≥40%. The overall study design is displayed in Figure 3-1.

Participants will be randomized in a 1:1 ratio to either finerenone or placebo. The study is designed to be able to show an effect on the primary endpoint with a power of 90% at an alpha level of 5%. It was originally anticipated that 5500 participants will be randomized and approximately 6900 will be screened (screening failure rate of approximately 20%). A total of approximately 2375 total (first and recurrent) primary composite events are targeted. Due to blinded event rates being lower than those assumed in the sample size calculation, the planned number of randomized participants was increased to approximately 6000. The target number of primary composite events was not changed.

The anticipated duration of the study will be approximately 42 months, with a recruitment period of 24 months. However, as an event-driven study, the actual length of the study will depend on the observed event rates, the participant recruitment rate, and the length of the recruitment period.

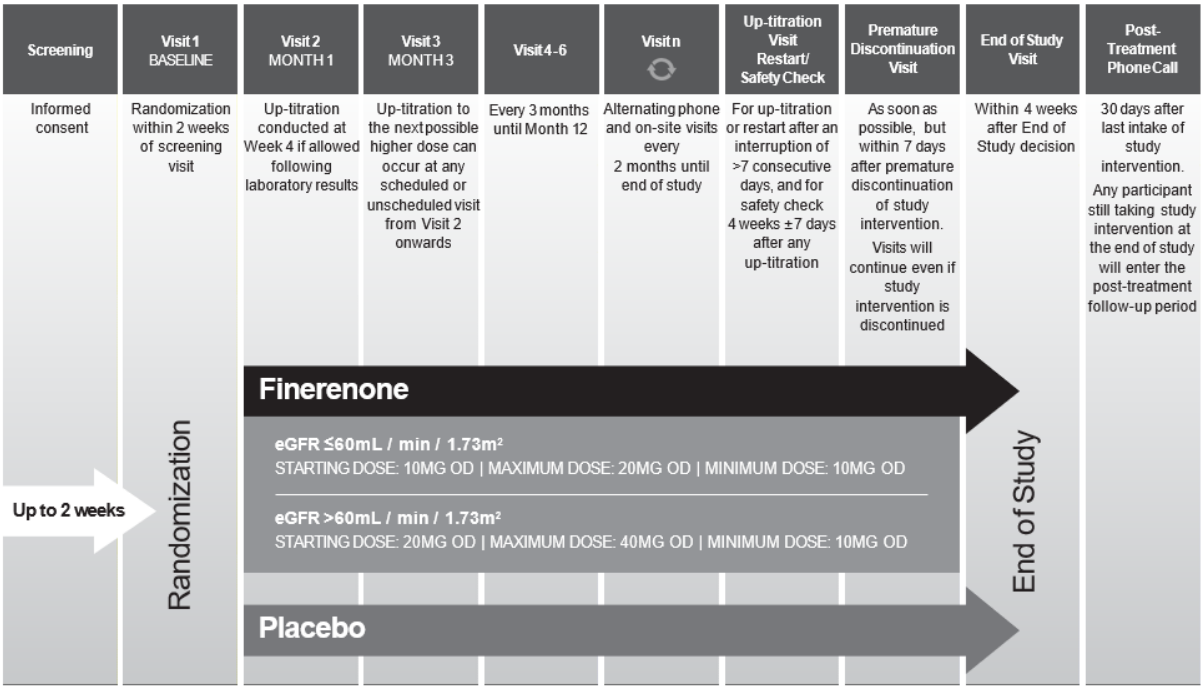
Enrolment in the trial may be capped based on the proportion of patients in certain LVEF categories, in each NYHA class, with/without atrial fibrillation, and by geographic region, among other variables, to ensure recruitment of a representative study population.

The randomization will be stratified by country/region and baseline LVEF (<60%, ≥60%).

Since all randomized participants (excluding those with critical GCP violations) belong to the Full Analysis Set (FAS) on which the efficacy analyses are based, it is important to avoid randomization of non-eligible patients into the study.

The general study design as applied to this study is shown in Figure 3-1. There is a screening period, a double-blind treatment period and a safety follow-up period. Patients prematurely terminating from the study and up to the primary study completion will be asked to attend scheduled visits to collect efficacy data.

Figure 3-1: Study design



Screening Visit

After providing written informed consent, a Screening Visit to confirm the participant's eligibility will take place prior to randomization. The Screening Visit may take place on the same day as randomization (Visit 1).

Treatment Period

Following a screening period of up to 2 weeks, eligible participants will be randomized in a 1:1 ratio to either finerenone or placebo. Participants with an eGFR ≤60 mL/min/1.73 m² measured at baseline will start with 10 mg once daily (OD) (**dose level 1**) with a maximum maintenance dose of 20 mg OD (**dose level 2**), whereas participants with an eGFR >60mL/min/1.73 m² measured at baseline will start with 20 mg OD (dose level 2) with a maximum maintenance dose of 40 mg OD (**dose level 3**).

There will be at least 2 scheduled visits within the first 3 months from randomization: Visit 2 will take place after 1 month and Visit 3 will take place 3 months after randomization; thereafter, scheduled visits will occur every 3 months until Visit 6 at Month 12. After 1 year from randomization, telephone contact visits will take place at Month 14 and from then onwards every 4 months (i.e. Month 18, Month 22, etc.) alternating with on-site visits (i.e. Month 16, Month 20, etc.) until the end of the study is reached.

Up-titration is expected to occur after 4 weeks ± 7 days of treatment at Visit 2 (Month 1). Ideally, each participant will be on the maximum maintenance dose at this point. In the event of elevated potassium values, participants will be down-titrated to the next lower dose. Down-titrations can be performed at any time after the start of study intervention treatment, at any scheduled or unscheduled visit. At any scheduled or unscheduled visit, the dose of study intervention may be increased to the next possible higher dose, based on serum/plasma potassium level and provided the participant was already on a stable dose for 4 weeks ± 7 days.

Participants will attend an additional unscheduled safety visit 4 weeks ± 7 days after each up-titration; potassium levels and renal function will be monitored at this safety visit. In addition to the protocol-specified visits, participants may be seen at any time throughout the study at the discretion of the investigator.

Any changes in the study intervention dose, including interruption/permanent discontinuation or restart of study intervention, must be recorded in the electronic case report form (eCRF).

It is planned that all randomized participants will remain in the study until either:

a. an instruction is received from the sponsor after the targeted number of primary endpoint events have occurred
or

b. the study is terminated prematurely at the recommendation of the independent DMC.

After randomization, study intervention discontinuation does not constitute the participant's withdrawal from the study, and all participants should continue to be followed up. All randomized participants, including any participant who experiences an event considered for the pre-specified primary or secondary endpoints, should continue to receive double-blinded treatment until the study is completed, provided there are no safety grounds for discontinuing treatment.

Post-treatment Follow-up Period

The period between a participant's last intake of study intervention and last visit in the study is referred to as the 'post-treatment follow-up period'.

In case of premature discontinuation of study intervention, participants are expected to continue to attend all protocol-specified study visits, and are expected to perform all scheduled assessments as described in the Premature Discontinuation Schedule of Assessment in the protocol.

Any participant still taking study intervention at the point of end of study will enter the post-treatment follow-up period after stopping study intervention at the End of Study (EoS) Visit. For these participants, this phase will last 30 (+5) days, and will end upon completion of the Post-Treatment Visit (a telephone call visit).

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

The analysis will be based on the Global Standard Tables (Version 4.0 or higher) and the Clinical Pharmacology Standards (CLIPS) (Version 1.2 or higher) where appropriate. Compound Standard Tables will be developed.

The validity of participants for allocation to various analysis sets will be assessed in an ongoing manner in blind review meetings and decisions will be documented in the blind review reports prior to unblinding.

A log-normal distribution is assumed for urinary creatinine and albumin, urinary albumin-to-creatinine ratio (UACR), and N-terminal prohormone B-type natriuretic peptide (NT-proBNP). For all other metric variables, a normal distribution is assumed. The distributional assumptions will be investigated and if necessary, nonparametric methods or transformation of the data will be considered.

All variables will be analyzed by descriptive statistical methods. The number of data available, mean, standard deviation (SD), minimum, median, and maximum will be calculated for metric data. The geometric mean, SD and coefficient of variation (CoV) will be provided instead of the arithmetic mean and SD for the variables where log-normal distributions are assumed, as follows:

$$CoV = \sqrt{\exp(SD_{ln}^2) - 1}$$

SD_{ln} being the standard deviation of the log-transformed values. Frequency tables will be generated for categorical data.

The laboratory parameter eGFR will be calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Levey et al., 2009) for all analyses specified in this SAP. For patients recruited in Japan, the Japanese formula adjustment will be applied (Horio et al., 2010).

All participants will be analyzed according to the planned treatment group in FAS per the intention-to-treat (ITT) principle. All participants will be analyzed according to the actual treatment in the Safety Analysis Set (SAF). If a participant receives both treatments due to a

bottle error, the treatment actually received for the majority of the time in the study will be used in SAF.

Only adjudicated outcome events will be used for analysis of the primary and secondary efficacy variables (except for sustained decrease in eGFR ≥50% relative to baseline over at least 4 weeks and sustained eGFR decline <15ml/min/1.73m^2 which will be derived from central laboratory measurements and not be adjudicated); Section 6.2.4 specifies how investigator-reported outcomes for these variables will be summarized. Outcome events for exploratory efficacy variables (e.g. non-fatal myocardial infarction, non-fatal stroke, etc.) will not be adjudicated.

The stratified analyses mentioned in this SAP will be conducted in consideration of the randomization stratification factors:

- LVEF: <60%, ≥60%
- Pooled region for stratified analyses: randomization will be stratified by country/region, for the analyses individual countries/regions will be combined into pooled regions as follows:
    - Western Europe and Oceania: Australia, Austria, Denmark, Germany, Israel*, Netherlands, New Zealand, United Kingdom
    - Southwestern Europe: Italy, Portugal, Spain
    - Central Europe: Czechia, Hungary, Poland, Slovakia
    - Southeastern Europe: Bulgaria, Greece, Romania, Turkey
    - Northeastern Europe: Finland, Latvia, Lithuania, Russia, Ukraine
    - Asia: China, Hong Kong, India, Japan, Malaysia, South Korea, Taiwan
    - North America: Canada, United States of America
    - Latin America: Argentina, Brazil, Colombia, Mexico

*Although not geographically located in Western Europe or Oceania, Israel has been included in this pooled region.

In case of issues (e.g. model convergence) with using these predefined pooled regions at the final analyses, the pooled regions may be further combined. Any such changes will be described in the CSR.

All participants will be analyzed according to their correct stratification category. In case of a large number of stratification errors (≥5% of all patients in the FAS), the primary analysis will also be repeated based on the stratification category used in the randomization as a sensitivity analysis.

In case a death cannot be clearly adjudicated as CV-related or non-CV related, it will be adjudicated as undetermined death. Undetermined deaths will be handled as non-CV deaths for the analysis, unless otherwise specified. Where applicable, the combined results of non-CV deaths and undetermined death will be displayed along with results for the individual categories.

4.2 Handling of Dropouts

A participant who has been randomized and discontinues study participation prematurely for any reason, either during study treatment or during post-treatment follow-up, is defined as a 'dropout', even if no study drug has been taken. Dropouts will not be replaced.

Data from participants who prematurely terminated the study will be used to the maximum extent possible.

The number of participants discontinuing the epochs, together with the primary reason for discontinuation, will be summarized as described in Section 6.1.1.

The number of participants who prematurely discontinue the study and / or study treatment for any reason, as well as the reasons for premature discontinuation of study and / or study treatment, will be reported. Kaplan-Meier plots for "patients still participating in study" and "patients still on study treatment" will be provided.

All dropouts and participants prematurely discontinuing study treatment will be evaluated with respect to

- baseline characteristics
- potential differences between the treatment groups in the proportion of participant withdrawals or in the timing of withdrawals
- the reasons for premature discontinuation of study and/or study treatment.

4.3 Handling of Missing Data

All missing or partial data will be presented in the subject data listing as they are recorded on the eCRF.

General Rules

When appropriate, the following rules will be implemented so as not to exclude participants or observations from statistical analyses due to missing or incomplete data.

Concomitant medications with missing start and stop date but flagged as being ongoing at a participant's final visit will be considered to have started prior to study medication start and ended after stopping of study medication. The start and end reference period will be imputed as "before" for the medication start and as "during/after" for the medication end.

In case of partially missing dates for interruptions or permanent stop of study medication intake, a 'worst-case' approach will be applied to impute the start and end dates of study medication intake as the earliest and latest possible dates, i.e.:

- first month of the year and/or first day of the month for a partially missing start date, and
- last month of the year and/or last day of the month for a partially missing end date.

If a participant died earlier than the imputed worst study medication end date, the death date will be taken as the study medication end date. However, if these imputations lead to a temporal overlap between different exposure date records, the imputed dates will be adjusted so that no overlap exists and the time on the higher dose is maximized. The date of first exposure to treatment is not expected to be missing as the patients are instructed by the investigator to take their first dose of study drug directly at Visit 1, but in the very rare case

that this date is not recorded, it will be imputed according to the rules outlined above for missing start dates, but not earlier than the randomization date.

When only partial dates are available for clinical events in the efficacy analysis, a median imputation rule will be used:

- For example if the day is missing and the month is July, then day 16 is chosen.
- If the number of potential values is even, the lower of the 2 middle numbers is taken. For example, if the day is missing and the month is June, then day 15 is imputed. The same rule applies if the day and month are missing, e.g. if the year is 2017 and the day and month are missing, 2nd July is used.
- In case the range of possible values is further restricted, e.g. because a patient is randomized in the month in which the day is missing or the participant died in the month in which the day is missing, the median in the restricted set of possible values is calculated. For example, if the clinical event occurred in June 2017 and the respective patient died on 11th June 2017, 6th June 2017 is imputed as the date of the clinical event.

In case a death date is completely missing, it will be imputed on the basis of the last known contact when the participant was still alive and the first known contact when the participant was dead (e.g. from the participant health status follow-up page) as the median of these two dates. As above, if the number of potential values is even, the lower of the two middle numbers is taken.

In case both a non-fatal clinical event and death have partially missing dates, then death takes precedence and will be imputed first according to the rules outlined above. This also applies for non-CV death.

However, given the importance of an accurate determination of the adjudicated event date in relation to randomization date for the time to event analysis, we would expect a minimal number of such missing dates.

A worst-case approach will be applied for determining whether an adverse event (AE) with partially missing dates is treatment-emergent or not, i.e. if it is possible that the AE start date is within a period of study drug intake +3 days (on or after study treatment start date and on or before study treatment end date + 3 days) then the AE is considered treatment-emergent.

If intensity of the AE is missing, the event will be considered as severe. If the drug relationship is missing, the event will be considered as being related to the study drug.

4.4 Interim Analyses and Data Monitoring

One non-binding interim analysis for futility is planned when approximately 30% (~710) of the required total number of primary endpoint events have been observed. If the observed rate ratio (RR) on the primary endpoint is above 0.95, the trial is planned to be stopped for futility. This gives a probability of approximately 69% to stop under the null hypothesis (i.e. no treatment effect on the composite of HHFs and CV deaths) and leads to a loss in power of less than 1% under the alternative hypothesis of the treatment effect assumed for the sample size determination. No adjustment for this loss in power will be made.

The futility analysis given above is considered to be non-binding, the DMC will be asked to also consider important secondary efficacy endpoints as well as safety in their assessment.

In addition, one formal interim analysis for efficacy is planned when approximately 2/3 (~1580) of the required total number of primary endpoint events have been observed.

If the interim analysis shows clear and consistent benefit in the finerenone treatment group, the DMC may recommend early study termination. The Haybittle-Peto rule will be used to guide the decision regarding early stopping of the study for success: a reduction of 3 standard deviations (of the test statistic) in the analysis of the primary efficacy endpoint (two-sided p-value <0.0027) at the interim analysis. In addition, a nominal significant effect on the CV death component should be present (two-sided p-value<0.05) at the interim analysis. Note: The criterion for CV death would not be considered to prove formal statistical significance, as it does not keep the alpha level. It has been added so that the trial is only stopped at the interim if there is at least a certain amount of evidence of a beneficial treatment effect on CV death.

See Section 4.7 for a detailed description of the testing procedure, including an adjustment of the significance level for the interim analysis.

If the study is stopped early, the primary analysis reported in the CSR will consider all events up to the participants' respective EoS visits as would have been the case if the study had not stopped early. A sensitivity analysis will take all events up to the interim analysis datacut date into consideration. For this sensitivity analysis, censoring dates after the datacut date will be reset to the datacut date.

A detailed plan for the routine DMC safety analyses and the interim analysis will be covered in the DMC charter, the analysis planned to be provided to the DMC will be described in a separate SAP with Tables, Listings and Figures (TLFs) attached to the DMC charter. The DMC will review the data in an unblinded manner, both for the routine safety tables and the interim analysis. There are no predefined stopping conditions for the ongoing safety monitoring of this trial. The statistical analysis for the DMC meetings will be performed by an independent statistical analysis center. The sponsor will oversee and discuss with the Steering Committee overall blinded event rates to ensure that they are in line with protocol assumptions. If overall event rates are lower than expected, consideration will be given to altering the study design, such as increasing the sample size or extending the study duration without knowledge of any treatment effect.

4.5 Data Rules

General data rules are described in this section, further data rules for specific parameters or analyses are specified in the respective subsections of Section 6.

4.5.1 Baseline Values

Baseline values will be defined as the last non-missing measurement before or on the day of randomization. If the last observation available prior to randomization is the measurement from the Screening Visit, this would be used as the baseline value. This also includes assessments from a local laboratory, if no assessment from the central laboratory prior to first intake of study drug is available. Otherwise baseline will be missing.

If more than one measurement was planned for a scheduled time point, for example blood pressure (BP) measurements and heart rate, the mean value of the last set of measurements per time point prior to randomization will be used as the baseline value. In case of repeated measurements for pre-treatment visits and Visit 1 (Day 1; baseline), the closest measurement prior to the randomization will be used for analysis instead of the scheduled measurements.

When the Screening and Baseline visits are performed on the same day for a participant, the following assessments (scheduled to be performed at both the Screening and Baseline visits) will only be performed once and the data will appear under Screening:

- NYHA class
- Vital signs
- Local lab potassium and creatinine
- Pregnancy test

Where necessary, these data will be considered in the derivation of baseline values per the rules above.

4.5.2 Change from Baseline

Change from baseline will in general be displayed as absolute change from baseline defined as the difference to baseline, i.e.:

Absolute change = Post baseline value – baseline value.

Some parameters will be additionally analyzed as relative change defined as

Relative change = 100 * [(post baseline value – baseline value) / baseline value].

For specific analyses, the relative decrease of a variable will be analyzed instead of the relative change. The relative decrease is equivalent to the negative of the relative change and defined as

Relative decrease = 100 * [(baseline value – post baseline value) / baseline value].

4.5.3 Time Window for Efficacy Events

Events for time to first / recurrent analyses (e.g. primary efficacy endpoint) will be counted from the day of randomization (planned at Visit 1) onwards until the EoS visit following the study termination decision, or until the date of EoS notification + 4 weeks, if the EoS visit has not been performed. In the event of premature discontinuation from the study with no subsequent follow-up information, events will be counted up to the day of the last visit when information on the component is available.

4.5.4 Annual Rate of Recurrent Events

The annual rate of a recurrent event for an individual patient is calculated as:

Annual rate = (Total number of events) / (Follow-up time (days) / 365.25)

4.5.5 Other Data Handling

Only the data provided by the central laboratory will be used for analysis; values from local laboratories will not be used in the statistical analysis unless otherwise specified and will be listed only. For example, as described above, local values will be used in the derivation of baseline, if no central measurement is available (cf. Section 4.5.1).

At all visits post-randomization and if not stated otherwise, only the values at scheduled measurements will be used for analysis.

For the derived visit “Any time post baseline” (applicable for efficacy) this will include any measurement after randomization, including unscheduled assessments. For the derived visit

"Any time on treatment" (applicable for efficacy), only assessments on or after study medication start date until 30 days after last study drug administration, including unscheduled assessments, will be considered. For safety, "Any time treatment-emergent" will include measurements on or after study medication start date until 3 days after last study drug administration, including unscheduled assessments.

For values which are < LLOQ (Lower limit of quantification), half the value of the LLOQ will be used for analysis. Differences between two values < LLOQ will be assigned values of 0. Ratios between two values < LLOQ will be assigned a value of 1. For values which are > ULOQ (Upper limit of quantification), the ULOQ will be used for analysis.

In case of non-normally distributed data, descriptive statistics other than minimum, maximum and median will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification. In tables showing descriptive statistics, where values below LLOQ are included, these descriptive statistics will be marked.

4.5.6 Subgroup Analyses

Exploratory subgroup analysis will be done for the primary and secondary efficacy variables. The subgroup analyses will include subgroups based on the stratification factors. The list of key subgroups (in addition to the stratification factors) and other subgroups analyzed is specified below. Analysis will include descriptive statistics, graphical display of estimated treatment effects with 95% confidence intervals (CIs) in a forest plot and a statistical test for interaction.

Subgroups based on stratification factors

- Pooled region for subgroup analysis (Western Europe, Oceania and Others; Eastern Europe; Asia; North America; Latin America); the subgroup Western Europe, Oceania and Others combines the groups Western Europe and Oceania and Southwestern Europe from the pooled region for stratified analyses. The subgroup Eastern Europe combines the groups Central Europe, Southeastern Europe, and Northeastern Europe from the pooled region for stratified analyses.
- LVEF (<60%, ≥60%)

Key subgroups

- Baseline serum potassium value (≤ 4.5, > 4.5 mmol/L)
- eGFR category at baseline (eGFR <60, ≥60 mL/min/1.73 m²)
- Atrial fibrillation at baseline electrocardiogram (ECG) (present, absent)
- Diabetes Mellitus at baseline (present, absent)
- Index HF event (very recent (≤ 7 days before randomization), recent (> 7 days – ≤ 3 months), > 3 months or no index HF event).

Other subgroups

- Race (white, black, Asian, other)
- Sex (male, female)
- Age (≤ median vs. > median)
- Baseline body mass index (BMI) (< 30 vs. ≥30 kg/m^2)

- Systolic blood pressure (SBP) at baseline (≤ median vs. > median)
- Angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) or angiotensin receptor-neprilysin inhibitor (ARNI) use at baseline (yes, no)
- Treatment with sodium-glucose transport proteins-2 inhibitor (SGLT-2i) (yes, no)
- NYHA functional class at baseline (II, III/IV)
- Baseline NT-proBNP (≤ median vs. > median)
- Baseline UACR (<30 vs. ≥30 mg/g)

For subgroups split by median, the FAS will be taken as reference population for derivation of median.

Individual country analyses, e.g. for Japan, required for regulatory purposes, will be included in a country-specific study SAP.

4.6 Blind Review

The results of the final data assessment will be documented in the final list of important deviations, validity findings and assignment to analysis set(s). Any changes to the statistical analysis prompted by the results of the review of study data will be documented in an amendment and, if applicable, in a supplement to this SAP.

4.7 Testing Procedure and Multiplicity Adjustment

If the interim analysis shows clear and consistent benefit in the finerenone treatment group (defined as two-sided p-value <0.0027 for the primary efficacy endpoint and two-sided p-value <0.05 for the CV death component at the formal interim analysis for efficacy) the DMC may recommend early stopping of the study for success (see Section 4.4 for full details).

If the study is stopped early for success: the final analysis for the primary endpoint will be performed at an overall two-sided significance level of 0.0027. Additionally, the secondary endpoints of:

- Total (first and recurrent) HF events
- Improvement in NYHA class from Baseline to Month 12
- Change from baseline to Month 6, 9 and 12 in TSS from KCCQ
- Time to first occurrence of composite renal endpoint

will be formally tested. The testing strategy of the secondary endpoints is as follows:

1. Total HF events will be tested at the 0.0027 two-sided significance level.
2. If the hypothesis of the secondary endpoint total HF events is rejected, the NYHA class and KCCQ endpoints will be tested using the Bonferroni-Holm procedure, i.e. if at least one of the hypotheses of the two endpoints NYHA class and KCCQ can be rejected at the two-sided (0.0027/2) significance level, the remaining of the two endpoints will be tested at the 0.0027 significance level.
3. If the hypotheses for all previous secondary endpoints are rejected, the composite renal endpoint will be tested at the 0.0027 significance level.

If the test for any endpoint produces a non-significant result, the testing of the remaining endpoints further down in the procedure will be performed in an explorative manner only.

Furthermore, the second component of the primary endpoint (CV deaths) will be tested at the 0.0027 two-sided significance level outside of the alpha-preserving procedure for the primary and other secondary efficacy endpoints (Total HF events, NYHA class, KCCQ, renal composite).

If the study is not stopped early for success: a group sequential design with a single interim analysis when 2/3 of the information is available with a stopping rule of two-sided $p < 0.00270$ would require a small adjustment to the alpha level at the final analysis to maintain the overall significance level at 0.05. For an information fraction of 2/3, the adjusted alpha level of 0.04967 applies. If the study is not stopped early for success a p-value of $p<0.04967$ is therefore required at the final analysis to achieve formal statistical significance.

If the primary hypothesis is rejected, the secondary endpoints of:

- Total (first and recurrent) HF events
- Improvement in NYHA class from Baseline to Month 12
- Change from baseline to Month 6, 9 and 12 in TSS from KCCQ
- Time to first occurrence of composite renal endpoint

will be formally tested with the following test strategy:

1. Total HF events will be tested at the 0.04967 two-sided significance level.
2. If the hypothesis of the secondary endpoint total HF events is rejected, the NYHA class and KCCQ endpoints will be tested using the Bonferroni-Holm procedure, i.e. if at least one of the hypotheses of the two endpoints NYHA class and KCCQ can be rejected at the two-sided (0.04967/2) significance level, the remaining of the two endpoints will be tested at the 0.04967 significance level.
3. If the hypotheses for all previous secondary endopints are rejected, the composite renal endpoint will be tested at the 0.04967 significance level.

If the primary hypothesis is not rejected, these tests will be performed in an explorative manner only; similarly, if the test for any secondary endpoint produces a non-significant result, the testing of the remaining endpoints further down in the procedure will be performed in an explorative manner only.

Furthermore, if the primary hypothesis is rejected then the second component of the primary endpoint (CV deaths) will also be tested at the 0.04967 two-sided significance level outside of the alpha-preserving procedure for the primary and other secondary efficacy endpoints (total HF events, NYHA class, KCCQ, renal composite).

Regardless of whether the study is stopped early for success: as a hard endpoint and objective indicator of benefit-risk, time to ACM will be tested at a two-sided significance level of 0.05, after the rejection of the primary hypothesis. Testing of time to ACM will thus be done outside of the alpha-preserving procedure for the primary and other secondary efficacy variables (total HF events, NYHA class, KCCQ, renal composite).

5. Analysis Sets

5.1 Assignment of Analysis Sets

Final decisions regarding the assignment of participants to analysis sets will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to analysis set(s) (see Section 4.6).

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the informed consent form (ICF)
Randomly assigned to study intervention	All participants randomly assigned to study intervention
Full analysis set (FAS)	All randomized participants. Participants will be analyzed according to the intervention they were randomized to. The only potential reasons for exclusion would be a clearly erroneously randomization, or major good clinical practice (GCP) violations, for example, a suspicion of fraud.
Safety analysis set (SAF)	All participants in the FAS who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic analysis set (PKS)	All finerenone-treated participants (with the exception of participants excluded on the grounds of critical GCP violations) with at least 1 valid finerenone plasma concentration and without validity findings which would interfere with the evaluation of the pharmacokinetic (PK) data.
Listing-only set	All participants enrolled who were not randomized or were excluded from the FAS. Their data is provided as individual participant data listings and will not be included in any statistical analyses.

6. Statistical Methodology

6.1 Population Characteristics

Population characteristic analyses, except for participant disposition, will be performed for the FAS, if not stated otherwise.

6.1.1 Disposition

The number of participants enrolled, randomized and valid for the FAS and SAF will be summarized overall and by treatment group, country/region and study site. The number of participants discontinuing each epoch, together with the primary reason for discontinuation will be presented by treatment group (post-randomization epochs only) and overall in separate tables. In addition, the number of participants with important deviations will be presented

overall, by country/region for each treatment group, and in total. The frequencies of each important deviation and validity finding will be presented by treatment group and in total.

6.1.2 Demography and Other Baseline Characteristics

Demography includes age (continuous and categorized by 40-<65, 65-<75, 75-<85, ≥85), sex, race, pooled region (for stratified analysis and for subgroup analysis), body weight (continuous and categorized by <60, 60-<90, ≥90 kg), body height, BMI (continuous and categorized by <30 vs. ≥30 as well as by <18.5, 18.5 to <25, 25 to <30, 30 to <35, ≥35 kg/m^2), hip and waist circumference and waist-hip ratio, smoking history (never, former, current smoker) and alcohol consumption.

Other baseline characteristics include baseline

- LVEF (continuous and categorized by <60% vs. ≥60% as well as <50, 50-<60, ≥60%)
- NYHA Class (II, III, IV)
- index HF event (randomized during/at HF event, very recent (≤ 7 days from randomization), recent (>7 days - ≤ 3 months), >3 months, no index; as well as ≤ 7 days from randomization, >7 days - ≤ 3 months, >3 months or no index event)
- type of (latest) index HF event with respective timing (hospitalization for heart failure, urgent HF visit, no index event)
- serum potassium (continuous and categorized by ≤4.5 mmol/L vs. >4.5 mmol/L)
- eGFR (calculated by CKD-EPI formula, Japanese formula adjustment made for participants recruited in Japan; continuous and categorized by <60 vs. ≥60 mL/min/1.73 m² as well as <45, 45 to <60, 60 to <90, ≥90 mL/min/1.73 m²),
- serum creatinine (continuous)
- SBP (continuous and categorized by <90, 90-<130, 130-<160, ≥160 mmHg)
- diastolic blood pressure [DBP] (continuous)
- heart rate (continuous)
- NT-proBNP (continuous)
- UACR (continuous and categorized by <30 vs. ≥30 as well as <30, 30-<300, ≥300 mg/g)
- history of LVEF<40% (yes [improved], no). For participants with a history of LVEF <40%, prior LVEF values will be summarized.
- Atrial fibrillation at baseline per ECG
- Diabetes Mellitus at baseline
- ACEI, ARB or ARNI use at baseline
- SGLT-2i use at baseline.

All demographic data and baseline characteristics will be tabulated by treatment group and overall. The demographic and other baseline characteristics table will also be presented, separated by each level of the stratification factors.

The non-stratified demographic and other baseline characteristics table will be repeated for the SAF if ≥5% of randomized patients do not take at least one dose of study intervention (i.e. are in the FAS but not the SAF).

As stated in Section 4.2, demographics and other baseline characteristics will also be presented separately for participants prematurely discontinuing the study and for participants permanently discontinuing study treatment.

6.1.3 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be presented for each MedDRA Primary System Organ Class (SOC) and Preferred Term (PT) by treatment group and overall in a summary table. Additional medical history terms by the following Standard MedDRA Queries (SMQs), Project-specific Bayer MedDRA Queries (PBMQs), Bayer MedDRA Labeling Groupings (MLGs) or selected PTs will also be presented:

- Hyperlipidemia (MLG)
- Hypertension (MLG)
- Type 2 diabetes mellitus (PT)
- Atrial fibrillation/flutter (PBMQ)
- Ischemic Stroke/Transitory Ischemic Attack (TIA) (PBMQ)
- Myocardial Infarction (MLG)
- Coronary Artery Disease (PBMQ)
- Peripheral Arterial Occlusive Disease (PBMQ)
- Cardiac Failure (MLG)
- Coronary Artery Bypass Graft (CABG) (PBMQ)
- Chronic Obstructive Pulmonary Disease (COPD) (PT)
- Percutaneous coronary intervention (PCI) (PBMQ)
- COVID-19 (SMQ narrow)
- Hepatic cirrhosis (PT)
- Sleep Apnea Syndrome (PT)
- Chronic Kidney Disease (CKD) (PT)

The medical history tables will be repeated for SAF.

6.1.4 Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). The number of participants who took at least one concomitant medication and the number of participants who took at least one medication that started before administration of study drug will be presented by treatment group and overall using anatomical therapeutic chemical (ATC) classes and subclasses.

These tables will be repeated summarizing the number of participants with medications in the Standard drug groups of interest. In addition, the number of participants who took at least one concomitant medication that started after start of study drug and the number of participants who took at least one medication ongoing at baseline (i.e. starting before or on the day of randomization and ending at least one day after the day of randomization) will be presented by treatment group and overall. Standard drug groups of interest are:

- ACEIs and ARBs
- ARNIs
- Beta-blockers
- Loop diuretics
- Thiazide diuretics
- Digoxin
- Nitrates
- Potassium supplements
- Potassium lowering agents (including binders)
- Alpha blocking agents
- Calcium channel blockers
- Centrally acting antihypertensives
- Strong, unclassified, moderate, weak cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors
- Strong, unclassified, moderate, weak CYP3A4 inducers
- Aspirin
- Statins
- MRAs
- Organic anion transporting polypeptides (OATP) substrates

Anti-diabetic drugs

- Insulin and analogues
- SGLT-2 inhibitors
- Other anti-diabetic drugs (Dipeptidyl Peptidase 4 inhibitors or Glucagon-like peptide-1 agonists or Biguanides or Sulfonylureas or Alpha glucosidase inhibitors or Metiglinides or Thiazolidinediones.)

A participant will be counted only once within each ATC class / subclass or Standard drug group, respectively.

A listing will be provided including all medications classified as a strong, unclassified, moderate, or weak CYP3A4 inhibitor according to the drug groupings together with the respective classification information.

For potassium lowering agents, ACEIs, ARBs, diuretics and SGLT-2 inhibitors shift tables for changes of use for baseline vs. any time treatment-emergent will be provided.

The number of participants with MRA use during follow-up will be given by substance.

6.1.5 Treatment and Study Duration, Extent of Exposure and Compliance

The analyses described in this section will be repeated for the SAF if ≥5% of randomized patients do not take at least one dose of study intervention (i.e. are in the FAS but not the SAF). All tables and figures regarding treatment duration, extent of exposure and compliance will be presented by treatment group and overall (unless otherwise stated).

Treatment duration, defined as time from start of study drug to permanent stop of study drug (in months), will be summarized using descriptive statistics by treatment group and overall. The total duration in patient-years will be provided. In addition, treatment duration will be categorized to ≤ 1 month, 1 – 3 months, >3 – 6 months, >6 – 12 months, and then further six-monthly intervals, and presented with the corresponding number and percentage of participants. Cumulative treatment duration will be categorized to at least one dose, at least 1 month, at least 3 months, then further 3 monthly intervals. A table will be presented with the absolute and relative frequencies of participants still on study medication at each visit. Kaplan-Meier plots for "patients still on study treatment" will be provided, as also described in Section 4.2.

The above analyses will be repeated for study duration, from the day of randomization to the EoS visit.

The extent of exposure to study drug (total amount of intake in grams) and the average daily dose in mg during treatment will be summarized using descriptive statistics by treatment group. The table will be repeated by participants starting on 10 mg and 20 mg, respectively.

The number and percentage of participants on each dose level (blinded) will be summarized by visit and treatment group, overall and differentiated by participants starting on 10 mg or 20 mg. The overall titration status, regardless of actual or sham up-titration, will be summarized with absolute and relative frequencies per treatment group, overall and differentiated by patients starting on 10 mg or 20 mg. In addition, the number of patients with study drug down-titrated or temporarily interrupted (dose recorded as 0 mg) as well as associated reason will be summarized with absolute and relative frequencies per treatment group, overall and differentiated by participants starting on 10 mg and 20 mg, respectively.

The overall compliance (as a percentage) will be calculated as follows:

100 * Number of tablets taken / Number of planned tablets.

The number of planned tablets will be calculated as follows:

(Days from randomization to last intake of study drug + 1) * Number of planned tablets per day.

For participants who withdraw prematurely from the study drug, compliance will be calculated up to the time of last dose.

The overall compliance will be summarized descriptively by treatment group and overall. In addition, percentage compliance will be categorized into three groups, less than 80%, 80 to 120% and greater than 120%, and the categories will be summarized by treatment group and overall.

6.2 Efficacy

6.2.1 Analysis of Primary Efficacy Variable

Events that could potentially fulfill the criteria for primary efficacy variables during the study will be evaluated by the CEC. Definitions of individual endpoints (e.g. CV death) will be provided in the Endpoint Manual.

6.2.1.1 Primary Efficacy Variable: Primary Analysis

The primary Estimand as defined in Section 2 will be used for the primary analysis. The primary endpoint is the composite of CV death and total (first and recurrent) HF events (HHF or urgent HF visit) in HF patients. The primary analysis of this endpoint will be performed in the FAS using the planned treatment group, in line with the ITT principle.

Participants without an event of the primary composite endpoint at the time of analysis will be censored at the date of their last contact or date of non-CV death.

The number and incidence rate of primary endpoint events and censoring events (i.e. non-CV death) will be summarized per treatment group, both overall and per individual event category. 95% CIs of the incidence rates will be derived based on a Poisson model with robust variance estimator.

The primary analysis of the primary composite endpoint will be based on a stratified Andersen-Gill model (Andersen, 1982) including treatment group as fixed effect and including pooled region for stratified analyses and baseline LVEF (<60%, ≥60%) as stratification factors. Robust standard errors (sandwich estimator) will be used to account for correlations of event times within a participant. As shown by Lin et al. 2000, the Andersen-Gill model with robust standard errors can be interpreted as a proportional rates model. After the authors of the paper, the model is also referred to as Lin, Wei, Yang and Ying (LWYY) model. Let θ be the RR for the finerenone versus placebo group. In order to evaluate whether finerenone is superior to placebo in reducing the rate of the composite event of CV death and total HF events the following null hypothesis will be tested using the model above (see Section 4.7 for details regarding the nominal significance level):

$$H_0: \theta = 1 \text{ versus } H_1: \theta \neq 1,$$

where $\theta < 1$ represents a treatment benefit of finerenone over placebo.

A point estimate of the RR together with a 95% CI will be presented alongside the point estimate and hazard ratio for the censoring event of non-CV death, calculated using a stratified Cox proportional hazards model.

The primary analysis method has been investigated with extensive simulation studies and it has been confirmed that it keeps the alpha level and has good operating characteristics across a range of plausible scenarios. A small adjustment will be made to the nominal significance level and the critical value at the final analysis to take into account the interim analysis (see Section 4.7 for details). No adjustment to the sample size calculation is done for this.

The SAS code below illustrates the program for the Anderson-Gill model:

```
PROC PHREG DATA=primary COVS(aggregate);
  MODEL (time_start, time_rec)*status(0)=treat/ties=efron rl;
  ID patid;
```

```
  STRATA {stratum};
RUN;
```

`primary` is the input dataset, `time_start` is the previous event stop time and `time_rec` is the current event stop time, the censoring variable `status` (0 for censored and 1 for event) should take the value 1 if the last event is a CV death and 0 if it is censored for a non-CV death or at the end of study for the given patient; `patid` is the participant ID and `treat` is the treatment group identifier.

If a participant experiences an HF event and subsequently dies for a cardiovascular reason, this will be considered as two separate events for the primary analysis unless the participant dies on the same calendar day as the HF event (both events would still be considered for the analyses of the separate components). If a participant is hospitalized for HF shortly after an urgent HF visit, this will be considered as two separate events for the primary analysis unless they occur on the same calendar day.

Additionally, plots and summaries of the mean cumulative function for the primary endpoint (Nelsen-Aalen estimate) will be presented by treatment group.

6.2.1.2 Primary Efficacy Variable: Sensitivity Analysis

As a sensitivity analysis, the number of primary composite events will also be analyzed using a negative binomial regression model including stratification factors and treatment group as covariates and log follow-up time as an offset parameter.

As a sensitivity analysis, plots and summaries of the mean cumulative function for the primary endpoint will be derived based on a competing-risk approach (Ghosh and Lin, 2000) and cumulative incidence function for the competing event of non-CV death (Aalen and Johansen, 1978) will be presented by treatment group. The following SAS Code illustrates the program for the mean cumulative function for the primary endpoint:

```
PROC PHREG DATA=primary;
  MODEL (time_start, time_rec)*event(0)= / eventcode=1;
  STRATA treat;
  ID patid;
  BASELINE OUT=mcfdat CIF=cif LOWERCIF=lcif UPPERCIF=ucif /
           SEED=999;
RUN;

DATA mcfdat;
  SET mcfdat;
  mcf = -log(1-cif)
  lmcf = -log(1-lcif)
```

```
  ucif = -log(1-ucif)
RUN;
```

`primary` is the input dataset, `time_start` is the previous event stop time and `time_rec` is the current event stop time, the event variable `event` (0 for censored, 1 for primary event, and 2 for competing event) and `patid` is the participant ID and `treat` is the treatment group identifier.

6.2.1.3 Primary Efficacy Variable: Supportive Analysis of CV death component

As part of the primary analysis, a separate estimate of the treatment effect for CV death as one of the components of the primary endpoint will be obtained. The second component of total HF events will be a secondary endpoint and analyzed as described in Section 6.2.2.1.

The main cause-specific treatment effect estimate for CV death will be derived from a stratified Cox proportional hazards model for time to CV death and the main p-value from a stratified log-rank test. A cause-specific treatment effect estimate for the censoring event of non-CV death will also be calculated using a stratified Cox proportional hazards model and presented with associated 95% confidence interval. The cumulative incidence functions for time to CV death and time to non-CV death will also be calculated using Aalen-Johansen estimates.

Note that the study is not powered to show an effect on CV death alone. While this is the case, a sufficient number of deaths are expected so that an excess risk in mortality can be excluded. Under the assumptions of the sample size determination, approximately 535 CV deaths and approximately 775 all-cause deaths are expected to occur in the study. Even though no formal statistical tests for exclusion of an increased risk will be performed, these expected event counts would result in a relatively high power to exclude increased hazard ratios (HRs) on ACM. Table 6–1 provides the respective power values to exclude HRs above 1.15 and 1.25 under different assumed values for the true HR on CV death and assuming no treatment effect on non-CV deaths (HR_{NonCVD}=1.0). Similar to the primary endpoint, a treatment policy strategy is used for treatment discontinuation. With exclusion of a certain HR value it is meant that the upper limit of a 95% CI is below the value.

Table 6–1: Power to exclude increased HR on ACM under different assumed treatment effects on CV death

True HR_{CVD}	Exclude HR_{ACM}>1.15	Exclude HR_{ACM}>1.25
0.8	94%	>99%
0.9	78%	97%
1.0	52%	88%

6.2.1.4 Primary Efficacy Variable: Supportive Analysis of Time-to first event of Composite Endpoint

As supportive analysis, stratified Cox proportional hazard regression analysis will be performed for the time to first composite of HF event or CV death and a plot of Aalen-Johansen estimates of the cumulative incidence function will be provided.

6.2.1.5 Primary Efficacy Variable: Other Supportive Analyses

A supportive analysis of the primary endpoint will exclude urgent HF visits and consider only CV deaths and HHFs as events. Also, an additional analysis of the primary endpoint will restrict CV deaths to HF-related events and thus will consider HF events and CV deaths due to HF. These analyses will both be performed for total (first and recurrent) events and for first events only.

A total-time approach considering times from randomization to the onset of first, second, third composite event using a Wei, Lin, and Weissfeld (WLW, 1989) model will be applied. This model enables analysis of the cumulative effect on the primary endpoint from randomization (i.e. the effect on second event includes the effect on the first, and the effect on third event includes the effects on the first and second). The corresponding individual HRs with 95% CIs comparing treatment groups on the first, second, and third event will be presented.

In addition, a conditional gap-time model according to Prentice, Williams and Peterson (PWP, 1981) will be applied to obtain HR estimates with 95% CIs for the time from first to second and from second to third event (note that this gives a non-randomized comparison). Both models will employ robust standard errors and include the stratification factors and treatment group as fixed effects. Both WLW and PWP approaches are known to have limitations and hence are strictly only performed as supplemental analyses since they aim at describing different aspects of recurrent events.

An "on-treatment" analysis will be performed, including only events occurring up to 30 days after treatment discontinuation. This analysis will be performed in the SAF instead of the FAS.

In addition, table and figure of risk ratios and respective confidence intervals will be provided for the primary efficacy endpoint with patients being censored sequentially at each study day similar to figure 3 in Packer et al. (2021). The first day where the upper CI of the RR is below 1 and stays below for the remainder will be marked.

The primary analysis for the primary endpoint will also be repeated for the "Total HF events and ACM" endpoint.

In addition, the primary analysis will also be repeated where patients are included with only up to a maximum of 4 composite events, to examine the impact of patients with a large number of events. For this analysis, patients who experienced 4 or more events will be censored at the time of their 4^{th} event.

An additional analysis of the primary endpoint will include a time-dependent covariate for SGLT-2 inhibitor use.

6.2.2 Analysis of Secondary Efficacy Variables

6.2.2.1 Secondary Efficacy Variables: Primary Analysis

Secondary efficacy variables are the following:

- Total (first and recurrent) HF events
- Improvement in NYHA class from Baseline to Month 12
- Change from baseline to Month 6, 9 and 12 in TSS of the KCCQ

- Time to first occurrence of composite renal endpoint: sustained decrease in eGFR ≥50% relative to baseline over at least 4 weeks, or sustained eGFR decline <15ml/min/1.73m^2 or initiation of dialysis or renal transplantation
- Time to ACM

See Section 4.7 for details regarding the testing hierarchy for secondary endpoints and nominal significance levels.

Total HF events will be analyzed in a similar fashion to the primary endpoint, using an LWYY model including treatment group as fixed effect and including pooled region for stratified analyses and baseline LVEF (<60%, ≥60%) as stratification factors. A treatment policy strategy will be applied for treatment discontinuation, i.e., all events and follow-up time will be included in the analysis; all-cause death will be a censoring event for a while-alive approach.

The percentage of participants with improvement in NYHA class from Baseline to Month 12 will be analyzed with a logistic regression model including factors for treatment group and stratification levels. A patient is considered as having improved in NYHA class, if the NYHA class at Month 12 (Visit 6) is at least one category improved compared to the baseline visit. A composite strategy will be applied to those cases, where no measurement at Visit 6 is available due to stop of treatment prior to Visit 6. That means these patients are considered to have not improved in NYHA class. Participants who are still in the treatment period at Visit 6, but have NYHA assessment missing, will be imputed by taking the mean of the last available measurement prior to Visit 6 and the first measurement thereafter. Participants with no further value available after Visit 6 or whose only available information is from EoS visit will be imputed as non-responders. Participants with missing baseline value will be excluded from the analysis. Odds ratio and two-sided 95% confidence intervals will be provided for the comparison of finerenone vs. placebo treatment group. In addition, change from baseline in NYHA class will be summarized descriptively using shift tables, presented by visit and any time post-baseline. These tables will present the number of participants with the class at a certain visit by their respective baseline class.

The absolute change from baseline including measurements up to Month 12 of the KCCQ TSS will be analyzed by a repeated measures mixed model including the factors treatment group, baseline, visit, baseline-by-visit interaction, and factors for the stratification levels. For each treatment group a separate covariance pattern will be estimated based on an unstructured covariance to adjust for within participant variance.

In case the model does not converge, different covariance patterns will be used, in the following order, until convergence is met: separate unstructured covariance patterns, separate Toeplitz covariance patterns, separate Autoregressive(1) covariance patterns, and finally separate Compound Symmetry covariance patterns will be used.

Differences between the finerenone and the placebo treatment groups will be calculated with two-sided 95% CIs. The comparison assumes a common treatment effect across Month 6, 9 and 12 and will be considered primary. This analysis will investigate the effect on the KCCQ TSS while patients are alive and irrespective of any permanent treatment discontinuation. This means that all observed values will be included in the analysis.

The primary analysis of the secondary time-to first event variables (i.e. composite renal endpoint and ACM) will be done with a stratified log-rank test for testing and a stratified Cox proportional hazards model for obtaining a point estimate with 95% CIs. The Cox proportional hazards model will be stratified according to the stratification factors and include

treatment group as fixed effect. For the composite renal endpoint, the cause-specific point estimate with 95% confidence interval for the censoring event of death will also be presented. Cumulative incidence function plots and summaries (calculated using Aalen-Johansen estimates) will be produced for the composite renal endpoint and the censoring event of death. In addition, components of the composite renal endpoint will be analyzed. Furthermore, Aalen-Johansen plots will be displayed for the ACM endpoint.

Only central laboratory measurements before initiation of dialysis or renal transplantation will be considered for the definition of the individual eGFR-based components of the renal endpoint. At the up-titration, restart and safety check visits, only a local laboratory measurement is obtained. These values will be checked for a potential eGFR event and, in case of decline, the investigators will be advised to retest eGFR centrally in an unscheduled visit; determination of an eGFR event will then be based on this value. If an initial decrease in eGFR occurs on the EoS visit, there will be another confirmatory measurement taken at least 4 weeks later to confirm the initial decrease. The individual components "Sustained decrease of eGFR ≥ 50% from baseline over at least 4 weeks" as well as "Sustained eGFR decline <15ml/min/1.73m^2" will be programmatically derived. Only in the event that the eGFR decrease was confirmed by at least one additional eGFR measurement taken at least 4 weeks later, it will be considered as a sustained decrease and counted for the renal endpoint. The confirmatory additional eGFR measurements will typically be taken during an unscheduled visit. The date used for the analysis will be the date of the initial sample exceeding the threshold. If there was no confirmatory assessment, events will only be counted for the renal endpoint when the patient died after the initial decrease or the patient went on renal replacement therapy such as dialysis or transplantation prior to their scheduled confirmatory assessment. If there is an intermediate measurement that does not confirm the initial decrease, the event will not be counted for the renal endpoint.

eGFR events will be counted from the day of randomization until the EoS visit (or EoS notification + 28 days if EoS visit is missing). Participants will be censored at the earliest of the date of their last visit when a central eGFR measurement is available or EoS visit date (or EoS notification + 28 days if EoS visit is missing). If no post-baseline eGFR measurement is available, participants will be censored at day 1 (randomization date).

The other two components of the renal composite endpoint, i.e. initiation of dialysis or renal transplantation, will be adjudicated. To account for events of initiation of dialysis or renal transplantation after the last eGFR is recorded at a clinic visit, such events will be included in the efficacy analysis of the composite renal endpoint if they occur in the period up to the next planned clinic visit (+ 1 month) or EoS visit date (or EoS notification + 28 days if EoS visit is missing) or death date or last contact date. If no post-baseline eGFR measurement is available, the next planned visit is the date of Visit 2 (Month 1). Censoring will be applied at the last eGFR date (or day 1 if last eGFR date is missing) or at the earliest of EoS visit date (or EoS notification + 28 days if EoS visit is missing) or death date or last contact date, if these occur earlier than the next eGFR date + 1 month.

Randomized participants without an event of the composite renal endpoint at the time of analysis will be censored at the latest censoring date of their individual components.

6.2.2.2 Secondary Efficacy Variables: Sensitivity Analysis

As a sensitivity analysis for the total HF events endpoint, a joint frailty model (Rogers et al., 2016) with constant baseline hazard for CV death and constant baseline intensity for HF events will be fitted including effects for treatment group, pooled region for stratified analyses

and baseline LVEF (<60%, ≥60%). A gamma frailty distribution will be assumed. This model gives a treatment effect on total HF events which is adjusted for a potential treatment effect on CV death. An effect on CV death might otherwise dilute the effect seen on the hospitalizations, i.e. an effective treatment will prevent CV deaths especially in the more severely ill participants, which then potentially results in many hospitalizations.

The joint frailty model can sometimes have convergence issues (Toenges & Jahn-Eimermacher, 2020); additionally, estimates obtained from the model have sometimes been observed as unstable (e.g., large differences with changes in starting values and/or ordering of covariates in the model). Should such problems be encountered, a simpler model including only treatment group as a fixed effect will be used instead. The joint frailty model additionally produces an estimate for CV death; however, this will be considered only supportive for the analysis of this component and instead the main analysis for the CV death component is described under the primary efficacy variable in Section 6.2.1.2.

6.2.2.3 Secondary Efficacy Variables: Supportive Analysis

As supportive analysis for the total HF events endpoint, stratified Cox proportional hazard regression analyses will be performed for the following endpoints and plots of Aalen-Johansen estimates of the cumulative incidence functions will be provided:

- Time to first HF event
- Time to first HHF
- Time to first urgent HF visit

The additional analyses of the secondary time-to-first event endpoints will include an "on-treatment analysis". For the renal composite endpoint, events will only be counted if they occur within 5 months after the last visit with complete information on all components of the composite primary endpoint. A 5-month time window is used as visits are 4-monthly and in order to allow for late attendance by an additional 1 month. The proportional hazards assumption will be investigated by plotting smoothed Schoenfeld residuals. For the renal endpoint, a time-to-first event analysis will be done separately for each of the components.

A supportive analysis of the KCCQ TSS will apply a worst-case imputation for death which means that if a patient dies, a worst score of 0 for the TSS will be imputed for all subsequent visits after the patient's death (i.e., composite strategy). Treatment effects at Month 6, 9 and 12 will also be investigated individually by adding a treatment-by-visit interaction into the model.

A responder analysis for the KCCQ TSS will also be performed, defining patients with an increase of ≥5 points from baseline to Month 12 (or, for those with a baseline score of >95, a score of >95 at Month 12 without decline from baseline) as a responder. All observed values will be included irrespective of any permanent treatment discontinuation. In case of missing data, a patient's last available post-baseline score prior to Month 12 will be used (i.e. while-alive strategy) unless the patient died before Month 12 in which case they will be imputed as a non-responder (i.e. composite strategy). Responder status will be analysed using a logistic regression model including treatment, baseline TSS and stratification factors as covariates; the odds ratio and associated 95% CI will be reported. This analysis will be repeated for cut-offs of ≥10 points increase from baseline to Month 12 (or maintaining a score of >90 from baseline to Month 12 without decrease from baseline) and ≥20 points increase (or maintaining a score of >80 without decrease from baseline). These cut-offs correspond to small (≥5), moderate (≥10) and large (≥20) clinically meaningful improvements (Spertus et al, 2005). A

further analysis will define those responders who do not experience a ≥5 points decrease from baseline (or, for those with a baseline score of <5, a score of ≥5 at Month 12). This is equivalent to not experiencing a small deterioration. The number and percentage of patients who are responders or non-responders per each of the above criteria will be presented at Months 6, 9 and 12. This will include a breakdown of the criteria met for response (e.g. increase from baseline of ≥5, >95 at baseline and post-baseline visit) or non-response (e.g. change from baseline of <5, >95 at baseline and ≤95 at post-baseline visit, missing score at post-baseline visit).

A second responder analysis for the KCCQ TSS will use the thresholds derived from the anchor-based analyses with the Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) for a clinically meaningful within-patient change in KCCQ TSS at month 6, 9 and 12, respectively, which have been performed separately on blinded data (cf. Section 6.2.3.1). The derived thresholds are

- Minimally important within-patient improvement: 9.09
- Moderate within-patient improvement: 19.85

These thresholds will be used for each timepoint.. All observed values will be included irrespective of any permanent treatment discontinuation. In case of missing data, a patient's last available post-baseline score prior to Month 6, 9 or 12, respectively, will be used unless the patient died before the respective scheduled visit in which case they will be imputed as a non-responder. Responder status will be analysed using a logistic regression model at each timepoint including treatment, baseline TSS and stratification factors as covariates; the odds ratio and associated 95% CI will be reported.

Empirical cumulative density functions will be plotted for Months 6, 9 and 12, with change from baseline in KCCQ TSS (+100 to -100, ordered from greatest possible improvement to greatest possible worsening) on the x-axis and proportion of participants achieving this change or greater on the y-axis. Separate curves will be presented for each treatment group.

6.2.3 Analysis of Further Exploratory Efficacy Variables

Other exploratory efficacy variables will be as follows:

- Time to first CV hospitalization
- Total number of CV hospitalizations
- Time to first all-cause hospitalization
- Total number of all-cause hospitalizations
- Time to first occurrence of the following composite endpoint: CV death or non-fatal CV event (i.e. non-fatal myocardial infarction, non-fatal stroke, or HHF)
- Time to first occurrence of the following composite endpoint: sustained decrease in eGFR ≥ 57% relative to baseline over at least 4 weeks, or sustained eGFR decline < 15 ml/min/1.73m^2 or initiation of dialysis or renal transplantation
- Change in eGFR from baseline
- Mean rate of change in eGFR slope and its subcomponents acute and chronic slope
- Change in UACR from baseline

- Days alive and out of hospital (DAOH)
- Time to new onset of atrial fibrillation
- Change in health-related quality of life summary scores from baseline measured by KCCQ and EuroQol Group 5-dimension 5-level questionnaire (EQ-5D-5L)

Exploratory time-to-event variables will be analyzed using the stratified log-rank test and the stratified Cox proportional hazards model. Plots of Aalen-Johansen estimates of the cumulative incidence function will be provided.

The total number of CV hospitalizations will be analyzed using an LWYY model, similarly to the primary efficacy endpoint, and will be summarized descriptively by treatment group together with the annual rate of CV hospitalizations. These summaries and analyses will be repeated for all-cause hospitalizations.

The absolute change from baseline in eGFR at each visit until Visit 10 (Month 24) will be analyzed by a repeated measures mixed model with the factors treatment group, baseline eGFR, visit, treatment-by-visit interaction, baseline-by-visit interaction, and factors for the stratification levels (pooled region for stratified analyses and LVEF). Differences between the finerenone and placebo treatment groups at each visit will be calculated, and corresponding two-sided 95% CIs will be computed. For each treatment group a separate covariance pattern will be estimated based on an unstructured covariance to adjust for the within participant variance. Change in logarithmized UACR from baseline will be analyzed in an identical fashion. Results will be back-transformed to the original scale so that ratios will be displayed in table outputs.

Frequency tables will be generated for the number and percentage of patients with a relative decrease in eGFR of ≥25%, ≥30%, ≥40%, ≥50% and ≥57% from baseline. The analysis will be performed for each visit and for any time post-baseline.

The rate of change of eGFR will be compared between the finerenone and the placebo group by estimating the total eGFR slope using available assessments from baseline to planned end of the treatment period. It is assumed that changes in the mean response can be expressed in terms of a linear trend, and the treatment effect can be expressed in terms of the difference in slope between finerenone and placebo. For the analysis of the total slope, the serial change in eGFR will be modeled using a two-slope linear spline mixed-effects model in which a fixed change point will be defined to separate acute and chronic eGFR slope at Month 3 (Section 2.1 of Vonesh et al. 2019). In addition to fixed effects for the treatment, time (continuous) and treatment by time interaction, the model will include fixed effects for the stratification factors and random effects for the intercept, acute slope (baseline to Month 3), and chronic slope (Month 3 to planned end of treatment period). An unstructured covariance will be used to model the between-participant errors. Within-participant errors are assumed to be homogenous. Linear contrasts will be constructed to estimate the acute, chronic, and total slope in eGFR. LS means and differences of the acute, chronic and total eGFR slope for finerenone and placebo group will be provided with 95% confidence intervals (and corresponding p-values for the differences).

DAOH will be summarized descriptively by treatment group; the number and percentage of DAOH with respect to total potential follow-up time will be provided alongside the number and percentage of days dead and days in hospital, including breakdown into type of death. These analyses will be performed overall and separately by the stratification factors (pooled region for stratified analyses and LVEF).

DAOH will be analyzed by an ANCOVA model including potential follow-up time, treatment group, and stratification factors as fixed effects. Potential follow-up time is defined as the time from randomization up to end of study or lost to follow-up or withdrawal date, in case the patient did not complete the study.

DAOH will be analyzed once considering the total potential follow-up time and once considering only the first year of follow-up.

For the KCCQ, 3 further summary scores (physical limitation score [PLS], clinical summary score [CSS] and overall summary score [OSS]) will be derived. For the KCCQ PLS, CSS and OSS, the absolute change from baseline including measurements up to month 12 of the KCCQ TSS will be analyzed by a repeated measures mixed model including the factors treatment group, baseline, visit, baseline-by-visit interaction, and factors for the stratification levels. Differences between the finerenone and the placebo treatment groups will be calculated with two-sided 95% CIs. In addition, descriptive statistics will be presented by visit and treatment group: number of observations, number of missing values, minimum, first quartile, mean, standard deviation, median, third quartile, and maximum, including the changes from baseline. The analyses for TSS are described in Section 6.2.2.

For the EQ-5D-5L, summary scores will be calculated from the 5 dimensions according to the scoring instructions from UK and the US (refer to the EQ-5D-5L User Guide (EuroQoL Group 2013) and to the EQ-5D Value Sets (Szende et al. 2007). The values and the changes from baseline of the summary scores and the EuroQol Group visual analogue scale (EQ VAS) will be summarized by treatment group and visit using the same descriptive statistics as for KCCQ.

6.2.3.1 Patient Global Impression of Change (PGIC) and Severity (PGIS)

A sub-population of approximately 1200 participants is being asked the following questions at baseline (PGIS only) and at Visit 4 (Month 6), Visit 5 (Month 9) and Visit 6 (Month 12):

- PGIC: the participant is asked to assess the degree of change in their HF symptoms compared to the start of the treatment using the following response options: much better, better, a little better, the same, a little worse, worse or much worse
- PGIS: the patient is asked to assess the current severity of their HF symptoms due to HF using the following response options: no symptoms, mild, moderate, severe or very severe

These questions will be used as an anchor to provide an estimate of clinically meaningful change in the KCCQ TSS. Details of the analysishave been described in a separate SAP. The analysis has been conducted on a blinded dataset and will be reported separately from the CSR.

6.2.4 Outcome Events Reported by the Investigators

Outcome events using the investigator-reported terms will be summarized by treatment group, using tables analogous to those for aEs. Only adjudicated outcome events will be used for the analysis of the primary composite endpoint. Adjudication of the secondary renal endpoint will be restricted to cases of initiation of dialysis or renal transplant. No adjudication will be done for events only included in an exploratory efficacy endpoint (e.g. non-fatal myocardial infarction) and therefore the investigator-reported events will be used in the analysis of those endpoints. An overall summary of all outcome events will be generated by treatment group.

The number of participants with all outcome events, outcome events from randomization up to 30 days after stop of study medication, post-treatment outcome events occurring more than 30 days after stop of study drug or after the EoS Visit and outcome events by maximum intensity will be summarized by treatment group using MedDRA terms grouped by Primary SOC and PT.

The incidence rate of outcome events per 100 patient-years will also be provided by treatment group using MedDRA terms grouped by Primary SOC and PT. The time under risk for the incidence rates is defined as the time from randomization until the first onset of the event or the last date of contact with the participant in case no such event is recorded.

Outcome events will be summarized separately in the CSR Section 8.2 tables.

6.3 Pharmacokinetics/pharmacodynamics

6.3.1 Pharmacokinetics

The finerenone plasma concentration versus time data collected at various study visits will be evaluated descriptively, separated by dose and visit. Plots will be prepared of all individual plasma concentrations vs. actual relative study times (time of sample collection after time of study drug administration).

Evaluation of the concentration data will be performed using Population Pharmacokinetic (PK) methods, followed by PK / Pharmacodynamic (PD) analyses. These analyses will be described in a separate Analysis Plan outside of this document and will be reported separately.

6.3.2 Pharmacodynamics

Analysis of the pharmacodynamics parameters (e.g. blood pressure, heart rate, laboratory values) will be described in detail in a separate SAP.

6.4 Safety

All analyses on safety and tolerability data will be performed in SAF.

6.4.1 Adverse Events

AEs will be coded using the latest version of MedDRA available prior to database freeze. A listing will be provided linking the original investigator terms and the coded terms. AEs will be presented grouped by SOCs and PTS.

AEs that occurred or worsened after the first dose of study drug and up to 3 days after the last dose of study drug will be considered as treatment-emergent AEs (TEAEs).

To comply with local regulatory requirements in Japan and India, certain cardiovascular disease-related outcome events will also be documented as (S)AEs in Japan and India. These will be included in the outcome event tables (see Section 6.2), and to avoid double-counting of such events, they will not be included in the adverse event summary tables or listings. Separate listings will be generated for all AEs excluded from the AE analysis due to double reporting in Japan and India, respectively.

An overall summary of all AEs, pre-treatment AEs, post-treatment AEs occurring more than 3 days after stop of study drug and TEAEs will be generated by treatment group. TEAEs and treatment-emergent SAEs will be summarized by subgroups as defined in section 4.5.6.

The number of participants with TEAEs, post-treatment AEs occurring more than 3 days after stop of study drug, treatment-emergent serious adverse events (SAEs), treatment-emergent study drug-related AEs, treatment-emergent study drug-related SAEs, TEAEs and treatment-emergent SAEs resulting in discontinuation of study drug, treatment-emergent study drug-related AEs resulting in discontinuation of study drug, treatment-emergent non-serious AEs, TEAEs and treatment-emergent SAEs by maximum intensity, drug-related TEAEs by maximum intensity, TEAEs and treatment-emergent SAE by worst outcome and drug-related TEAEs by worst outcome will be summarized by treatment group using MedDRA terms grouped by Primary SOC and PT.

Hyperkalemia and worsening of renal function are considered events of special safety interest. Hyperkalemia will be defined by MLG 'Hyperkalemia' and worsening of renal function will be defined by

- List of PTs: 'Acute kidney injury', 'Blood creatinine increased', 'Glomerular filtration rate decreased', 'Postrenal failure', 'Prerenal failure', 'Renal failure' and 'Renal impairment'
- SMQ 'Acute renal failure' (narrow search)
- SMQ 'Acute renal failure' (broad search).

An overall summary for each definition of worsening of renal function as well as for hyperkalemia will provide the number of participants once for all events and once for all treatment-emergent events by treatment group.

In addition, further safety variables listed in Section 9.4.2 of the protocol are:

- Number of participants with hospitalization for hyperkalemia
- Number of participants permanently discontinuing study intervention due to hyperkalemia
- Number of participants with hospitalization for worsening of renal function
- Number of participants permanently discontinuing study intervention due to worsening of renal function

These will be summarized for treatment-emergent events by treatment group using frequency counts and grouped by Primary SOC and PT.

Cumulative incidences based on Aalen-Johansen estimates and accounting for mortality as competing risk will be provided for the time to first treatment-emergent hyperkalemia event. For this analysis, the person-time at risk for a single participant is the number of days from first intake of study intervention until the event of interest or until the minimum of (date of death, last exposure to treatment + 3 days). Since the number of particpants with hospitalization or permanently discontinuing study intervention due to hyperkalemia is very low, no cumulative incidences will be displayed for these variables.

For hyperkalemia AEs, an additional sensitivity analysis will be performed where events are defined as treatment-emergent, if the AE started or worsened after the first dose of study drug up to 3 days after any temporary or permanent interruption of study drug.

The incidence of TEAEs and treatment-emergent SAEs per 100 person-years will also be provided by treatment group using MedDRA terms grouped by Primary SOC and PT. This analysis will consider the first AE per Primary SOC or PT for a participant. Per SOC or PT, the incidence per 100 person-years will be derived as

100 * (number of participants with TE(S)AE) / (sum of time at risk).

The time at risk per patient is defined as time from first dose of study drug to last dose of study drug + 3 days (treatment-emergent), or death, if earlier, for those patients without a respective AE. For patients with AE, it is the time from first dose of study drug to AE start date. In case the AE start date is (partially) missing, the earliest possible date will be imputed; i.e. first day of a month, first month of a year, restricted to date of first study drug intake.

In case of events with different intensity within a participant, the maximum reported intensity will be used. If intensity is missing, the event will be considered as severe. If the same event is reported as both unrelated and related to the study drug within a participant, the event will be considered as related to study drug. If the drug relationship is missing, the event will be considered as being related to the study drug. Deaths and SAEs will be listed separately.

Any AEs/SAEs related to study procedure recorded after signing of informed consent but prior to randomization will be tabulated separately.

6.4.2 Laboratory Parameters

Generally, only central laboratory measurements will be used for analyses. The only exception is for hematology, where a few countries have the possibility to use local labs in exceptional circumstances (e.g. logistical challenges due to global pandemic, natural disaster, or regional crisis). These local measurements will also be used for the analysis.

The number of participants with treatment-emergent (after the first dose of study drug and up to 3 days after last dose of study drug) abnormal laboratory values above or below the normal range will be tabulated by the laboratory parameter and treatment group.

Summary statistics including changes to baseline will be calculated by treatment group and visit for all quantitative laboratory parameters, e.g. for hematology, NT-proBNP, high sensitive troponin T (hs-TNT), clinical chemistry and urinalysis. Geometric statistics and ratios to baseline will be presented for urinary creatinine, albumin and UACR and NT-proBNP instead of arithmetic statistics with changes from baseline. For eGFR the relative change will be displayed in addition to the absolute change from baseline. Graphical displays will be provided for change from baseline and ratio to baseline by visit, respectively. Proportion of patients with available and missing measurements will also be displayed.

Summary statistics for serum potassium, eGFR, NT-proBNP and serum creatinine will also be repeated by treatment group and visit separately for each level of the stratification factors.

The following special safety parameters will be further assessed by displaying the number of participants with safety events as described below by treatment group, visit and for any time treatment-emergent (including unscheduled assessments) and up to 3 days after last study drug administration. This will also be performed by stratification factors. The summaries will be performed for the number of participants with:

- Absolute value of serum potassium >5.0 mmol/L, >5.5 mmol/L (hyperkalemia), >6.0 mmol/L (severe hyperkalemia) and >7.0 mmol/L
- Relative decrease from baseline in eGFR of ≥25%, ≥30%, ≥40%, ≥50% and ≥57%, also sustained decrease over 4 weeks
- Absolute value of eGFR < 30 ml/min/1.73m²
- Increase from baseline in serum creatinine >0.3 mg/dL and >0.5 mg/dL.

The percentage of participants with the respective events (non-stratified) at any time post-baseline (including unscheduled assessments) and within 3 days after last study drug administration will be compared between the finerenone and placebo group by applying separate explorative χ^2 tests with continuity correction. If the expected number of participants in at least 1 cell of the 2x2 contingency table is <5 (Agresti 2005), Fisher's exact test will be applied instead of the χ^2 test. Estimates and two-sided 95% CIs will be provided for each treatment group and the treatment differences. Clopper-Pearson CIs will be calculated for each treatment group, while for treatment differences the exact unconditional confidence limits will be calculated.

6.4.3 Other Additional Safety Variables

6.4.3.1 Vital Signs

At the corresponding visits, 2 BP and 1 pulse measurements of vital signs parameters will be taken. Averages of non-missing values of these two BP measurements will be calculated and used for the statistical analysis. If only one of the planned measurements is available, this value will be used.

Vital signs values will be summarized by treatment group and visit using descriptive statistics including absolute changes from baseline. Changes from baseline will also be displayed graphically. The analysis will be repeated for SBP stratified by baseline SBP ≥90 to <130 mmHg, 130 to <160 mmHg and ≥160 mmHg.

6.4.3.2 Weight and BMI

The values and the changes from baseline will be summarized by treatment group and visit using descriptive statistics for weight and BMI.

6.5 COVID-19 and Related Issues

It is expected that the COVID-19 pandemic – ongoing at the start of the trial (14-Sep-2020) – will have some impact on this trial. Every effort will be made to capture the effect of COVID-19 on the study conduct. All adjudicated outcome events will additionally be adjudicated for relationship to COVID-19 (yes, possibly, no). COVID-19 related study disruptions comprise missing visits or procedures, study drug interruptions or permanent discontinuations, AEs related to COVID-19, and (other) protocol deviations and will be analysed as follows:

- All patients affected by study disruption related to the COVID-19 pandemic will be listed together with site information and the type of study disruption(s)
- Number of patients affected, number of missed visits, number and type of protocol deviations will be tabulated
- COVID-19 pandemic related reasons (participant decision, physician decision, or logistical reasons) for premature discontinuation of study epochs (e.g., screen failure, discontinuation of study drug, etc.) and changes in study treatment (e.g., dose titration, interruption, discontinuation, etc.) will be included in the relevant summaries
- Coded terms for COVID-19 will be included in medical history and adverse event summaries

Supportive analyses to evaluate the impact of the COVID-19 pandemic on the primary analysis will be conducted for the primary and secondary efficacy endpoints.

The primary analysis of the primary and secondary endpoints mostly follows the treatment policy strategy as described in ICH E9 (ICH 2019), in which participants are analyzed as they were intended to be treated and all relevant data are used regardless of any previous intercurrent events like COVID-19 infections or study drug interruptions which could have an influence on the occurrence of the event of interest. Only the following intercurrent events are handled with different approaches:

Endpoint	**Intercurrent events and strategies**
Primary endpoint (CV death and total HF events)	Non-CV death is treated as a censoring event for a while-alive strategy. Additionally, CV death is counted as both an outcome event as well as a censoring event, hence a combination of composite and while-alive strategy
Total HF events	Non-CV death is treated as a censoring event for a while-alive strategy. Additionally, the effect on total HF events is adjusted for a potential treatment effect on CV death
Improvement in NYHA class from Baseline to Month 12	A composite strategy is applied when no measurement is available at Month 12 (due to death, or other reasons)
Change from baseline to Month 6, 9 and 12 in TSS from KCCQ	All observed values up to death for any cause are included, i.e. a while-alive strategy is used
Time to first occurrence of renal composite endpoint	All-cause death is treated as a censoring event for a while-alive strategy. If a participant had a decrease or decline in eGFR but died before a confirmatory eGFR measurement could be taken, then the event is counted for the analysis
Time to ACM	Not applicable

This general approach is still considered valid despite the presence of the COVID-19 pandemic, considering the following factors:

- COVID-19 related study disruptions are expected to be equally likely to occur in either treatment group, therefore not creating bias for the treatment effect
- Information on most adjudicated endpoint events can still be collected even when physical visits cannot take place although incidences or reporting of some adjudicated events might change, e.g. as fewer participants might be hospitalized and have a higher risk of death

To quantify the impact of the COVID-19 pandemic, the following supplemental analyses will be performed:

- Primary endpoint (CV death and total HF events)
    - To address the hypothetical scenario in which participants did not experience any study disruption due to the COVID-19 pandemic, three separate analyses

will be conducted using the LWYY model described in Section 6.2.1.1 where participants are censored at

a) Date of permanent discontinuation of study treatment due to COVID-19

b) Date of first COVID-19 adverse event (SMQ narrow)

c) Date of first direct or indirect COVID-19 study disruption

This analysis will be performed once including all primary efficacy events and once excluding those events adjudicated as related to COVID-19. For the latter analysis, the affected participants will be censored at the first occurrence of a COVID-19 related event

Additionally, plots and summaries of the mean cumulative function for the primary endpoint (Nelsen-Aalen estimate) will be presented by treatment group.

- To investigate the effect of COVID-19 related study disruption on the results of the primary analysis, a time-dependent covariate capturing whether a participant is affected by COVID-19 at the respective time together with its interaction with treatment group will be included in the LWYY model described in Section 6.2.1.1. Separate models will be used for the three COVID-19 related categories described above (permanent discontinuation of study treatment, AEs, and study disruption). Events occurring before and after participants are affected by COVID-19 will also be summarized by treatment group
- Primary efficacy events (CV death and HF events) and the competing event of non-CV death will be summarized by treatment group and relationship to COVID-19 as adjudicated by the CEC, defined as follows:
  - Yes (positive testing, typical clinical trajectory)
  - Possibly (inconclusive or absent testing, typical clinical trajectory)
  - No (testing negative or not done, not suspected)
- If ≥5% of the total number of primary efficacy events are adjudicated as "Yes" or "Possibly" related to COVID-19, a further analysis using the LWYY model will be performed excluding such events; the affected participants will be censored at the first occurrence of a COVID-19 related event
- Primary efficacy events occurring during interruption of study treatment (due to COVID-19, or due to other reasons) up to 30 days after any temporary or permanent stop of study treatment will be summarized by treatment group

- Total HF events
  - Summaries of HF events occurring before and after participants are affected by COVID-19, and during interruption of study treatment, will be included as part of the summaries for the primary endpoint described above
- Improvement in NYHA class from Baseline to Month 12
  - Reasons for a participant being classified as "not improved" at Month 12 under the composite strategy will be summarized, including:

  - NYHA measured at Month 12 and not improved from baseline
  - NYHA not measured at Month 12 due to COVID-19 related reason
  - NYHA not measured at Month 12 due to other reason
- Change from baseline to Month 6, 9 and 12 in TSS from KCCQ
  - No additional summaries or analyses are proposed. This endpoint will be analyzed by a repeated measures mixed model which is valid under the missing at random assumption, and COVID-19 related study disruptions are expected to be equally likely to occur in either treatment group and therefore not related to study treatment
- Time to first occurrence of renal composite endpoint
  - Events occurring before and after COVID-19 related study disruption, and during study treatment interruptions due to COVID-19 or other reasons, will be summarized by treatment group
- Time to ACM
  - To address the hypothetical scenario in which participants were not affected by the COVID-19 pandemic, the stratified log-rank test and stratified Cox proportional hazard model as described in Section 6.2.2.1 will be repeated excluding any death adjudicated as "Yes" or "Possibly" related to COVID-19; these participants will instead be censored at the date of death. Aalen-Johansen plots for non-COVID and COVID related deaths will also be displayed

6.6 Regional crisis between Russia and Ukraine and Related Issues

During the conduct of the FINEARTS-HF study, the conflict between Russia and the Ukraine escalated in February 2022 and, as of finalization of this amendment of the SAP, the regional crisis is ongoing in Ukraine. Every effort will be made to capture the effect of this regional crisis on study conduct.

Crisis-related study disruptions comprise missing visits or procedures, study drug interruptions or permanent discontinuations, AEs related to the regional crisis, and (other) protocol deviations and will be summarized as follows:

- All patients affected by study disruption related to the regional crisis will be listed together with site information and the type of study disruption(s)
- Number of patients affected, number of missed visits, number and type of protocol deviations will be tabulated
- Crisis -related reasons (participant decision, physician decision, or logistical reasons) for premature discontinuation of study epochs (e.g., screen failure, discontinuation of study drug, etc.) and changes in the study treatment (e.g., dose titration, interruption or discontinuation of study drug, etc.) will be included in the relevant summaries
- AEs related to the regional crisis will be included in the relevant summaries; if possible, these will be identified and highlighted in the CSR

See Section 6.5 (COVID-19 and Related Issues) or individual analysis sections for a description of the intercurrent event strategies for the primary and secondary endpoints.

Similarly to the impact of COVID-19, the general approach for these endpoints is still considered valid despite the presence of the regional crisis, considering the following factors:

- Crisis-related study disruptions are expected to be equally likely to occur in either treatment group, therefore not creating bias for the treatment effect
- Information on most adjudicated endpoint events can still be collected even when physical visits cannot take place although incidences or reporting of some adjudicated events might change

Despite this, it is recognized that issues arising from the regional crisis (including but not limited to missing data, data of compromised quality and crisis-triggered intercurrent events) may have a substantial impact on individual data points, patients, sites and/or countries. Therefore, the situation will be monitored on an ongoing basis and a final decision will be made prior to unblinding as to whether specific data-handling rules are required for individual data points, patients, sites and/or countries. This decision will be documented in an SAP amendment or – if that is not possible – a note to file, and all rules will be described and justified in the CSR. Additional summaries and sensitivity analyses may also be required, and these will be reported in the CSR.

For example, due to substantial impact of the regional crisis on a specific site, a decision may be made to censor all study participants from that site at a specific date (e.g. 24-Feb-2022, recognized as the date that the conflict escalated).

Regardless of any decision to implement data-handling rules for data affected by the regional crisis, the following supplemental analyses will be performed to quantify the impact of the regional crisis:

- Primary endpoint (CV death and total HF events)
    - To address the hypothetical scenario in which Ukraine participants did not experience any study disruption due to the regional crisis, two separate analyses will be conducted using the LWYY model described in Section 6.2.1.1 where Ukraine participants are censored at
        a) Date of first direct or indirect crisis-related study disruption (missed assessment, missed visit, study drug interruption or permanent discontinuation due to the regional crisis)
        b) 24-Feb-2022, recognized as the date that the conflict escalated (date of the television broadcast “On conducting a special military operation” by Russian president Vladimir Putin)

      Additionally, plots and summaries of the mean cumulative function for the primary endpoint (Nelsen-Aalen estimate) will be presented by treatment group.
    - To investigate the effect of regional crisis related study disruption on the results of the primary analysis, a time-dependent covariate capturing whether a Ukraine participant is affected by the regional crisis the respective time together with its interaction with treatment group will be included in the LWYY model described in Section 6.2.1.1 Separate models will be used for the two dates described above. Events occurring before and after participants

are affected by the regional crisis will also be summarized by treatment group (separately for FAS and for Ukraine participants in the FAS only)
    - Primary efficacy events occurring during interruption of study treatment (due to the regional crisis, or due to other reasons) up to 30 days after any temporary interruption or permanent discontinuation of study treatment will be summarized by treatment group (separately for FAS and for Ukraine participants in the FAS only)
- Total HF events
    - Summaries of HF events occurring before and after participants are affected by the regional crisis, and during interruption of study treatment, will be included as part of the summaries for the primary endpoint described above
- Improvement in NYHA class from Baseline to Month 12
    - Reasons for a participant being classified as "not improved" at Month 12 under the composite strategy will be summarized, including:
        - NYHA measured at Month 12 and not improved from baseline
        - NYHA not measured at Month 12 due to crisis-related reason
        - NYHA not measured at Month 12 due to other reason
- Change from baseline to Month 6, 9 and 12 in TSS from KCCQ
    - No additional summaries or analyses are proposed. This endpoint will be analyzed by a repeated measures mixed model which is valid under the missing at random assumption, and crisis-related study disruptions are expected to be equally likely to occur in either treatment group and therefore not related to study treatment
- Time to first occurrence of renal composite endpoint
    - Events occurring before and after crisis-related study disruption, and during study treatment interruptions due to regional crisis or other reasons, will be summarized by treatment group (separately for FAS and for Ukraine participants in the FAS only)
- Time to ACM
    - Events occurring before and after crisis-related study disruption, and during study treatment interruptions due to regional crisis or other reasons, will be summarized by treatment group (separately for FAS and for Ukraine participants in the FAS only)

7. Document history and changes in the planned statistical analysis

- SAP version 0.4 dated 16 DEC 2019: unsigned draft version for special protocol assessment (SPA) submission
- SAP version 1.0 dated 04 SEP 2020
- SAP version 2.0 dated 24 FEB 2023
- SAP version 3.0 dated 20 JUN 2024

7.1 Overview of Changes to SAP – from version 1.0 to version 2.0

Description of the finerenone program in DKD is updated.

Primary and secondary objectives of the trial are moved from Section 3 to Section 2. Description of the primary Estimand is moved from Section 6.2.1.1 to Section 2. A figure of the testing procedure is included.

Total (first and recurrent) HF events is elevated from supportive analysis of the primary endpoint to a new secondary endpoint. Supportive analyses of the primary endpoint concerning only HF events are moved accordingly to become supportive analyses of the new secondary endpoint. This is based on changes made to the secondary endpoints in protocol V3.0

Improvement in NYHA class from Baseline to Month 12 is elevated from exploratory endpoint to new secondary endpoint. A logistic regression analysis is newly specified for the endpoint accordingly in accordance with protocol V3.0.

The composite renal secondary endpoint is changed to include sustained decrease in eGFR ≥50% relative to baseline instead of ≥40% in accordance with protocol V3.0.

Additional separate SAPs are mentioned for specific analyses (pooled analyses, scientific SAP).

Increase in sample size from 5500 randomized to 6000 randomized is described.

Handling of death adjudicated as undetermined death is clarified for the analyses.

Clarification of use of local laboratory values for analysis.

Clarification of definition of on-treatment analysis for efficacy vs. treatment-emergent analysis for safety is aligned throughout the document.

Subgroups are revised (pooled region; baseline eGFR; index HF event; age; BMI; SBP; ACEI/ARB/ARNI), additional subgroup is included (Baseline UACR) and some ‘other’ subgroups are removed (weight; MRA, beta-blocker, diuretic, anti-diabetics, potassium, CYP3A4 or Entresto use; history of CAD; Baseline hs-TNT).

The testing procedure and multiplicity adjustment is adjusted to reflect the two new secondary endpoints in accordance with protocol V3.0.

Demography and baseline characteristics are revised to ensure consistency with subgroups yet keeping baseline characteristics that are not any more used for subgroup analyses.

Inclusion of additional specific medical history terms (COVID-19, Liver cirrhosis, Sleep Apnea Syndrome, Chronic Kidney Disease) and clarification of derivations (via e.g. PT, MLG, etc).

Remove concomitant BCRP substrate use from concomitant medications of interest.

Additional tables for exposure and titration by starting dose have been specified.

Analysis strategies for the primary endpoint and secondary endpoints are revised to include the handling of censoring events. This concerns the primary endpoint, the supportive analysis of CV death, as well as secondary and exploratory time-to event endpoints.

Summary of incidence rate of primary endpoint events has been included.

Handling of multiple primary endpoint events (i.e. ‘7-day’ rule) has been revised to a ‘same calendar day’ rule. The supportive analysis on the ‘7-day’ rule has been removed accordingly.

Ghosh and Lin competing risk approach for the mean cumulative function has been moved to sensitivity analysis and respective example SAS Code for the mean cumulative function has been included.

Sensitivity and supportive analyses for the primary efficacy variable have been structured in separate sections (Section 6.2.1.2: Sensitivity and Section 6.2.1.3 to Section 6.2.1.5: Supportive). For the secondary endpoint of total HF events, a separate section with sensitivity analysis is included as well.

An additional sensitivity analysis with LVEF as continuous variable has been specified for the primary efficacy endpoint.

Further supportive analyses for the primary efficacy endpoint have been included (restriction to HF-related CV death; sequential censoring; time-dependent covariate of SGLT2-inhibitor use).

The analysis of the secondary endpoint of total HF events is changed from a joint frailty model (as specified in protocol V3.0) to the LWYY model. A joint frailty model with constant baseline hazard for CV death and constant baseline intensity for HF events was instead included as sensitivity analysis. This change in analysis strategy is based on potential convergence issues and unstable estimates of the joint frailty model.

Additional model specification is included for the repeated measures model of the change in KCCQ TSS.

An additional sensitivity analysis with LVEF as continuous variable has been specified for the total HF endpoint.

Analyses with joint frailty models as supportive analyses of recurrent HHFs and recurrent urgent HF events have been removed.

A responder analysis based on thresholds of the anchor-based analyses with the PGIS/PGIC are included for KCCQ TSS. Empirical cumulative density functions are included for change from baseline in KCCQ TSS.

Time to first occurrence of a new composite renal endpoint including sustained decrease in eGFR ≥57% relative to baseline, mean rate of change in eGFR slope, and change in UACR from baseline are included as new exploratory endpoints and respective analyses of these endpoints are specified.

Additional model specification is included for the repeated measures model of the change in eGFR and UACR.

Exchanging analysis of AEs by SMQs with MLGs.

Handling of SAE and outcome events for Japan and India have been clarified.

Inclusion of analyses for hyperkalemia and acute renal failure.

Clarification of derivation of incidences per 100 person-years.

Handling of local hematology measurements due to local protocol amendment has been clarified.

Revision of cutoffs for special safety parameters.

Listing further safety variables in line with protocol.

Inclusion of further analyses for COVID-19 related issues.

Inclusion of analyses due to regional crisis between Russia and Ukraine.

A new section on document history and changes is included as this is required to document respective changes from the first version.

7.2 Overview of Changes to SAP – from version 2.0 to version 3.0

Removed reference to older protocol versions.

Clarification of log-normality assumption for specific parameters added.

Specification for the derivation of median for subgroup splits included.

Updated definition of SAF – clarifying excludion of participants with GCP violation.

Included definition of listing-only participants.

Removed ‘ethnicity’ from demography as not being collected in the study. Included a further category of <90 for SBP categorization, due to respective observed values.

Updated PT Term from ‘Liver cirrhosis’ to ‘Hepatic cirrhosis’.

Restricted some analyses on concomitant medications to medications in the standard drug groups of interest.

Separated CYP3A4 inhibitors and inducers.

Removed analysis of mean daily dose of MRAs due to unclean data.

Included total treatment duration in patient-years.

Removed analyses with continuous covariate of baseline LVEF as well as analysis with time by treatment interaction for primary and secondary endpoints.

Updated definition of ‘on-treatment’ in general and for renal composite endpoint specifically.

Included information on handling time after the forth event for analysis of the first 4 composite events.

Included further imputation rules for secondary endpoint ‘Improvement in NYHA class'.

Rules for usage of covariance patterns in case of non-convergence included for MMRM analysis of KCCQ TSS.

Updated the information on censoring for the renal endpoint and specifically for the different components.

Clarified intercurrent event strategies for KCCQ responder analyses.

Included thresholds for clinically meaningful change derived from separate anchor analysis.

Clarified analysis of UACR used log-transformation.

Removed breakdown of hospitalizations for DAOH.

Removed MedDRA Labelling Groupings analyses for Adverse events. Included further analyses for AEs by SOC and PT. Included analyses of AEs by subgroups.

The section 6.4.3.3 Further Safety Variables has been integrated into Advere Events Section 6.4.1 with further details included on the definition of Hyperkalemia and Worsening renal function events.

Included display of cumulative incidences for TE hyperkalemia events.

Updated list of lab parameters to be analyzed with geometric statistic (i.e. assuming log-normal data). Included graphical displays for lab parameters.

Included graphical displays for vital signs.

Minor wording updates throughout the document (e.g. changed ‘conflict’ to ‘regional crisis’; ‘subject’ to ‘participant’) and correction of typos.

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9. Appendix

9.1 The Kansas City Cardiomyopathy Questionnaire Scoring Instructions

There are 10 summary scores within the KCCQ, which are calculated as follows:

1. Physical Limitation

- Code responses to each of Questions 1a-f as follows:

  Extremely limited = 1
  Quite a bit limited = 2
  Moderately limited = 3
  Slightly limited = 4
  Not at all limited = 5
  Limited for other reasons or did not do = <*missing value*>

- If at least three of Questions 1a-f are not

  missing, then compute

  Physical Limitation Score = 100*[(mean of Questions 1a-f actually answered)

  – 1]/4 *(see footnote at end of this document for explanation of meaning of*

  "actually answered")

2. Symptom Stability

- Code the response to Question 2 as follows:

  Much worse = 1
  Slightly worse = 2
  Not changed = 3
  Slightly better = 4
  Much better = 5
  I've had no symptoms over the last 2 weeks = 3

- If Question 2 is not missing, then compute

  Stability Score = 100*[(Question 2) – 1]/4

3. Symptom Frequency

- Code responses to Questions 3, 5, 7 and 9 as follows:

  <u>Question 3</u>
  Every morning = 1
  3 or more times a week but not every day = 2
  1-2 times a week = 3

Less than once a week = 4
Never over the past 2 weeks = 5

Questions 5 and 7
All of the time = 1
Several times a day = 2
At least once a day = 3
3 or more times a week but not every day = 4
1-2 times a week = 5
Less than once a week = 6
Never over the past 2 weeks = 7

Question 9
Every night = 1
3 or more times a week but not every day = 2
1-2 times a week = 3
Less than once a week = 4
Never over the past 2 weeks = 5

- If at least two of Questions 3, 5, 7 and 9 are not missing, then compute:

  S3 = [(Question 3) – 1]/4
  S5 = [(Question 5) – 1]/6
  S7 = [(Question 7) – 1]/6
  S9 = [(Question 9) – 1]/4

  Symptom Frequency Score = 100*(mean of S3, S5, S7 and S9)

4. Symptom Burden

- Code responses to each of Questions 4, 6 and 8 as follows:

  Extremely bothersome = 1
  Quite a bit bothersome = 2
  Moderately bothersome = 3
  Slightly bothersome = 4
  Not at all bothersome = 5
  I've had no swelling/fatigue/shortness of breath = 5

- If at least one of Questions 4, 6 and 8 is not missing, then compute

  Symptom Burden Score = 100*[(mean of Questions 4, 6 and 8 actually answered) – 1]/4

5. Total Symptom Score

= mean of the following available summary scores: Symptom Frequency Score

Symptom Burden Score

6. Self-Efficacy

- Code responses to Questions 10 and 11 as follows:

Question 10
Not at all sure = 1
Not very sure = 2
Somewhat sure = 3
Mostly sure = 4
Completely sure = 5

Question 11
Do not understand at all = 1
Do not understand very well = 2
Somewhat understand = 3
Mostly understand = 4
Completely understand = 5

- If at least one of Questions 10 and 11 is not missing, then compute Self-Efficacy Score = 100*[(mean of Questions 10 and 11 actually answered) – 1]/4

7. Quality of Life

- Code responses to Questions 12, 13 and 14 as follows:

Question 12
It has extremely limited my enjoyment of life = 1
It has limited my enjoyment of life quite a bit = 2
It has moderately limited my enjoyment of life = 3
It has slightly limited my enjoyment of life = 4
It has not limited my enjoyment of life at all = 5

Question 13
Not at all satisfied = 1
Mostly dissatisfied = 2
Somewhat satisfied = 3
Mostly satisfied = 4
Completely satisfied = 5

Question 14
I felt that way all of the time = 1
I felt that way most of the time = 2
I occasionally felt that way = 3
I rarely felt that way = 4
I never felt that way = 5

- If at least one of Questions 12, 13 and 14 is not missing, then compute

Quality of Life Score = 100*[(mean of Questions 12, 13 and 14 actually answered) – 1]/4

8. Social Limitation

- Code responses to each of Questions 15a-d as follows:

Severely limited = 1
Limited quite a bit = 2
Moderately limited = 3
Slightly limited = 4
Did not limit at all = 5
Does not apply or did not do for other reasons = <*missing value*>

- If at least two of Questions 15a-d are not missing, then compute

Social Limitation Score = 100*[(mean of Questions 15a-d actually answered) – 1]/4

9. Overall Summary Score

= mean of the following available summary scores: Physical Limitation Score
Total Symptom Score
Quality of Life Score
Social Limitation Score

10. Clinical Summary Score

= mean of the following available summary scores: Physical Limitation Score
Total Symptom Score

Note: references to "**means of questions actually answered**" imply the following.

f If there are *n* questions in a scale, and the participant must answer *m* to score the scale, but the participant answers only *n-i*, where *n-i* >= *m*, calculate the **mean of those questions** as
(sum of the responses to those *n-i* questions) / (*n-i*) **not**
(sum of the responses to those *n-i* questions) / *n*