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STUDY DESIGN

Finerenone in patients with heart failure with mildly reduced or preserved ejection fraction: Rationale and design of the FINEARTS-HF trial

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Aim

Steroidal mineralocorticoid receptor antagonists (MRAs), spironolactone and eplerenone, are strongly recommended in the treatment of patients with chronic heart failure (HF) with reduced left ventricular ejection fraction (LVEF), but the balance of efficacy and safety in those with higher LVEF has not been well established. Broad use of steroidal MRAs has further been limited in part due to safety concerns around risks of hyperkalaemia, gynecomastia, and kidney dysfunction. These risks may be mitigated by the unique pharmacological properties of the non-steroidal MRA finerenone. The FINEARTS-HF trial is designed to evaluate the long-term efficacy and safety of the selective non-steroidal MRA finerenone among patients with HF with mildly reduced or preserved ejection fraction.

Methods

FINEARTS-HF is a global, multicentre, event-driven randomized trial evaluating oral finerenone versus matching placebo in symptomatic patients with HF with LVEF ≥40%. Adults (≥40 years) with HF with New York Heart Association class II–IV symptoms, LVEF ≥40%, evidence of structural heart disease, and diuretic use for at least the previous 30 days were eligible. All patients required elevated natriuretic peptide levels: for patients in sinus rhythm, N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥300 pg/ml (or B-type natriuretic peptide [BNP] ≥100 pg/ml) were required, measured within 30 days (in those without a recent worsening HF event) or within 90 days (in those with a recent worsening HF event). Qualifying levels of NT-proBNP or BNP were tripled if a patient was in atrial fibrillation at screening. Estimated glomerular filtration rate <25 ml/min/1.73 m^2 or serum potassium >5.0 mmol/L were key exclusion criteria. Patients were enrolled irrespective of clinical care setting (whether hospitalized, recently hospitalized, or ambulatory). The primary endpoint is the composite of cardiovascular death and total (first and recurrent) HF events. The trial started on 14 September 2020 and has validly randomized 6001 participants across 37 countries. Approximately 2375 total primary composite events are targeted.

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Conclusions The FINEARTS-HF trial will determine the efficacy and safety of the non-steroidal MRA finerenone in a broad population of hospitalized and ambulatory patients with HF with mildly reduced or preserved ejection fraction. Clinical Trial Registration: ClinicalTrials.gov NCT04435626 and EudraCT 2020-000306-29.

Keywords Heart failure with mildly reduced ejection fraction • Heart failure with preserved ejection fraction • Mineralocorticoid receptor antagonists • Worsening heart failure

Introduction

Activation of the mineralocorticoid receptor (MR) by aldosterone has long been recognized as a central driver of heart failure (HF) pathogenesis.[1] Mechanistically, ligand binding to the nuclear MR triggers a diverse signalling cascade contributing to excess salt and water retention, systemic hypertension, endothelial dysfunction, and pathological fibrosis, hypertrophy, and inflammation of the end organs, including the heart and kidneys.[2] These core mechanisms of disease progression appear operative in HF irrespective of ejection fraction. Hyperaldosteronism may in fact be frequently under-recognized at the population level,[3] including among those with established HF across the ejection fraction spectrum. Inhibition of this pathway with steroidal MR antagonists (MRAs), such as spironolactone and eplerenone, extends survival and prevents worsening HF events in patients with HF with reduced ejection fraction (HFrEF).[4,5] Global guidelines thus strongly recommend the use of steroidal MRAs as a core pillar of medical therapy in the management of HFrEF.[6,7]

In contrast, the role of MRAs remains less well established in patients with HF at higher ejection fractions. The TOPCAT trial evaluated spironolactone in patients with HF with preserved ejection fraction (HFpEF) in a large global population, but failed to show benefit with regard to its primary endpoint.[8] *Post hoc* analyses revealed important regional heterogeneity in study conduct, protocol adherence, clinical profiles, event rates, and efficacy of spironolactone with potential treatment benefits observed in participants enrolled from North and South America.[9,10] US guidelines now provide a weak recommendation for use of spironolactone in patients with HF with mildly reduced ejection fraction (HFmrEF) and HFpEF, while the European Society of Cardiology guidelines support consideration of steroidal MRAs in HFmrEF but not in HFpEF.[6,7]

The broader use of steroidal MRAs like spironolactone in HF has been limited, even in subpopulations with a strong evidentiary base for its use.[11] Suboptimal uptake of steroidal MRAs might in part be due to safety concerns, namely hyperkalaemia,[12] that may stem from the kidney-preferential tissue distribution of these therapies. Risks of treatment-attendant hyperkalaemia and other adverse effects in TOPCAT appear heightened in older adults[13] and patients with coexisting chronic kidney disease (CKD).[14] An analysis combining patients from RALES, EPHESUS and TOPCAT showed a stepwise increase in the odds of developing worsening of kidney function by 1.2 to 2.0 fold with steroidal MRAs as kidney function declined.[15] Especially in these high-risk populations, the risk–benefit profile of spironolactone may be unfavourable warranting judicious use under careful monitoring.

Finerenone is a non-steroidal MRA that is more selective for the MR than spironolactone or eplerenone and has a balanced tissue distribution in the heart and kidneys, which might lessen risks of electrolyte disturbances.[16] Two large-scale paired phase 3 clinical trials demonstrated that finerenone is safe and effective in slowing kidney disease progression and preventing cardiovascular events in over 13 000 patients with CKD and type 2 diabetes.[17,18] While <10% of participants in these trials had established HF and those with symptomatic HFrEF were excluded, finerenone significantly reduced risks of hospitalization for HF by 22% over a median follow-up of 3 years.[19,20] As such, finerenone presents a new opportunity to modify risk of adverse events in patients with HF, including among those with cardio-kidney-metabolic multimorbidity.

In a phase 2 trial of HFrEF and moderate CKD, finerenone 10 mg once daily and 5 mg twice daily were similarly effective as spironolactone 25 or 50 mg once daily in reducing natriuretic peptides and albuminuria, but with less hyperkalaemia/increases in blood potassium levels and less worsening kidney function.[21] In another, larger phase 2 trial in high-risk patients with worsening HFrEF and CKD and/or diabetes, short-term use of finerenone (2.5 mg to 20 mg once daily) versus eplerenone (25 mg every other day to 50 mg once daily) was well-tolerated with similar proportions of patients achieving clinically meaningful reductions in natriuretic peptide levels and similar effects on serum potassium.[22] In exploratory analysis, there was a lower risk of clinical events with the highest dose tested of finerenone compared with eplerenone, that reached nominal statistical significance.[22] *Table 1* provides an overview of completed phase 2 and 3 trials evaluating finerenone.

The potential advantages of the selective non-steroidal MRA finerenone over the steroidal MRA spironolactone and ongoing uncertainty about the role of MR antagonism in HF with higher ejection fractions provide rationale for a large outcome trial of finerenone in HF with mildly reduced or preserved ejection fraction. Here, we describe the design of the FINEARTS-HF (FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure) trial.

Trial design and methods

FINEARTS-HF is a global, multicentre, placebo-controlled, event-driven randomized clinical trial investigating the long-term efficacy and safety of the non-steroidal MRA finerenone in symptomatic patients with HF with LVEF ≥40%. The trial was designed collaboratively by members of

Table 1 **Completed trials of the non-steroidal mineralocorticoid receptor antagonist finerenone in patients with heart failure or chronic kidney disease**

	Phase 2 trials			Phase 3 trials	
Design elements	**ARTS**	**ARTS-HF**	**ARTS-DN**	**FIDELIO-DKD**	**FIGARO-DKD**
Sample size	65 (Part A) 392 (Part B)	1066	823	5734	7437
Starting finerenone dosing	2.5–10 mg once daily (Part A) 2.5–10 mg once daily or 5 mg twice daily (Part B)	2.5–15 mg once daily	1.25–20 mg once daily	10 or 20 mg once daily	10 or 20 mg once daily
Comparator	Spironolactone, placebo	Eplerenone	Placebo	Placebo	Placebo
Follow-up	28 days	90 days	90 days	2.6 years (median)	3.4 years (median)
Population	HFrEF and CKD	HFrEF and T2D and/or CKD	CKD and T2D	CKD and T2D	CKD and T2D
Primary endpoint	Change in serum potassium (Part B)	>30% decline in NT-proBNP	Change in UACR	Kidney failure, ≥40% decline in eGFR, or renal death	CV death, non-fatal MI, non-fatal stroke, or HF hospitalization
Summary of primary results	Finerenone 10 mg once daily and 5 mg twice daily led to greater mean increases in serum potassium, but this was lower than that observed with spironolactone (Part B)	Similar proportions of NT-proBNP declines were observed in finerenone and eplerenone arms	Dose-dependent reduction in UACR were observed with finerenone	Finerenone reduced risk of CKD progression by 18%	Finerenone reduced risk of composite CV events by 13%

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio.

the steering committee and the sponsor. The trial has been registered on ClinicalTrials.gov (NCT04435626) and EudraCT (2020-000306-29).

Eligibility criteria

Final inclusion and exclusion criteria are summarized in *Table 2*. In brief, FINEARTS-HF enrolled adults (≥40 years) with symptomatic HF (New York Heart Association class II–IV) with diuretic requirement at least 30 days prior to randomization. LVEF ≥40% and evidence of structural heart disease (left atrial enlargement or left ventricular hypertrophy) were required and could be measured locally by any modality within 12 months of screening. Left atrial diameter ≥3.8 cm, left atrial area ≥20 cm^2, or left atrial volume index >30 ml/m^2 qualified as left atrial enlargement. Left ventricular mass index ≥115 g/m^2 (if male) or ≥95 g/m^2 (if female) or septal or posterior wall thickness ≥1.1 cm qualified as left ventricular hypertrophy. Enrolment of patients with prior LVEF <40% with subsequent improvement to ≥40% was permitted provided that ongoing HF symptoms were present. The subgroup of patients with LVEF ≥60% was capped at a maximum of 20% of participants in the trial. All patients were required to have elevated natriuretic peptide levels, with eligibility thresholds adjusted based on the timing of recent HF events and the presence of atrial fibrillation. For patients in sinus rhythm, N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥300 pg/ml (or B-type natriuretic peptide [BNP] ≥100 pg/ml) were required, measured within 30 days (in those without a recent worsening HF event) or within 90 days (in those with a recent worsening HF event). Qualifying levels of NT-proBNP or BNP were tripled if a patient was in atrial fibrillation at screening. A worsening HF event could include either a hospitalization for HF or an urgent visit for HF. An eligibility flowchart is presented in online supplementary *Appendix S1*.

Patients could be enrolled irrespective of clinical care setting (whether hospitalized, recently hospitalized, or ambulatory). The proportion of patients without a recent worsening HF event within 3 months of randomization was capped globally at approximately 50% of the original planned sample size.

Recent myocardial infarction or any event that may result in reduced LVEF within 90 days of randomization was an exclusion criterion, although patients could be screened for eligibility after this window as long as they met other eligibility criteria. Specific cardiomyopathies or cardiac pathologies that might have distinct management approaches (such as amyloidosis) were excluded. Estimated glomerular filtration rate (eGFR) <25 ml/min/1.73 m^2 or serum/plasma potassium >5.0 mmol/L at screening or randomization were key exclusion criteria. These thresholds are aligned with current labelling (for CKD and type 2 diabetes) including by the US Food and Drug Administration for when finerenone is not recommended. Recent treatment with an MRA within 12 months of screening was not permitted, and discontinuation of an MRA for the purposes of study enrolment was discouraged.

All participants signed informed consents for participation and the study protocol was approved by the ethics committees and institutional review boards of each participating site. The trial started on 14 September 2020 and has validly randomized 6001 participants across 634 sites in 37 countries. The study is being conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

Study design

Following a screening period of up to 2 weeks, eligible participants were randomized in a 1:1 ratio to either finerenone or matching placebo (*Figure 1*). Starting dose was selected based on baseline eGFR. Participants with an eGFR ≤60 ml/min/1.73 m^2 started 10 mg once daily with a maximum maintenance dose of 20 mg once daily, whereas participants with an eGFR >60 ml/min/1.73 m^2 started 20 mg once daily with a maximum maintenance dose of 40 mg once daily (online supplementary *Appendix S1*).

Subsequent follow-up included two scheduled visits within the first 3 months of randomization, and then visits every 3 months until 1 year. After 1 year, telephone follow-up will alternate with on-site visits every 2 months until the end of the trial. After the completion of the randomized phase, any participant still taking the study drug will enter a post-treatment follow-up period for 30 days.

Dose titration and monitoring of safety and tolerability

The study aimed to encourage reaching and sustaining the maximum tolerated maintenance dose of the study drug. Blood measurements of potassium and creatinine were performed serially at study visits to capture pre-specified safety events including hyperkalaemia and worsening renal function. Up-titration is expected to occur any time after 4 weeks based on serum/plasma potassium level and if eGFR does not decline ≥30% compared to last scheduled visit. Down-titration may occur at any time if potassium ≥5.5 mmol/L and temporarily interrupted if already at the lowest dose. Temporary interruption of study drug and rechecking potassium levels within 72 h were recommended if potassium ≥6.0 mmol/L. Suggested management and dose adjustment in response to changes in potassium and renal function are detailed in online supplementary *Appendix S1*. Potassium-lowering therapies are permitted as per the investigator's discretion to be used during treatment with the assigned study drug.

Study objectives

The primary objective is to demonstrate the superiority of finerenone to placebo in reducing the rate of the composite of cardiovascular death and total (first and recurrent) HF events (HF hospitalization or urgent HF visit). A HF hospitalization was defined as a hospital admission lasting at least 24 h in length for the primary diagnosis of HF. An urgent HF visit was defined as an urgent, unscheduled ambulatory or emergency room visit for the primary diagnosis of HF requiring intravenous diuretic or vasoactive agent or mechanical or surgical intervention for HF. While oral diuretic intensification alone would not qualify for an urgent HF visit, analyses related to diuretic changes during the trial have been prespecified in the Academic Statistical Analysis Plan. The secondary objectives will be to determine the superiority of finerenone to placebo for each secondary endpoint: total HF events; improvement in NYHA class from baseline to month 12; change from baseline to month 6, 9 and 12 in the Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS); time to first occurrence of composite renal endpoint (defined as sustained decrease in eGFR ≥50% relative to baseline over at least 4 weeks, or sustained eGFR decline <15 ml/min/1.73 m^2, or initiation of dialysis or renal transplantation); time to all-cause mortality; and the safety and tolerability of finerenone (*Figure 2*).

Protocol amendments

All protocol amendments made to date are summarized in online supplementary *Appendix S1*.

Table 2 Detailed FINEARTS-HF inclusion and exclusion criteria

Study population	Patients with a diagnosis of HF, NYHA class II–IV, and documented LVEF of ≥40%.
Inclusion criteria	Participants are eligible to be included in the study only if all of the listed criteria apply.
Age	Participant must be aged ≥40 years at the time of signing the informed consent.

Type of participant and disease characteristics	• Diagnosis of HF with NYHA class II–IV, ambulatory or hospitalized primarily for HF (if a hospitalized patient cannot be randomized as an inpatient, randomization as soon as possible after discharge is encouraged).
	• On diuretic treatment for at least 30 days prior to randomization.
	• Documented LVEF ≥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.
	• Structural heart abnormalities based on any local imaging measurement within the last 12 months, latest at screening, defined by at least one of the following findings: LAD ≥3.8 cm, LAA ≥20 cm^2, LAVI >30 ml/m^2, LVMI ≥115 g/m^2 (in males)/95 g/m^2 (in females), septal thickness or posterior wall thickness ≥1.1 cm.
	• NT-proBNP ≥300 pg/ml (BNP ≥100 pg/ml) in sinus rhythm and the 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 the patient has an ongoing diagnosis of paroxysmal atrial fibrillation) for participants obtained at the following time:
	  • Within 90 days prior to randomization if the patient had been hospitalized for HF requiring initiation or change in HF therapy or if the patient had an urgent visit for HF requiring IV diuretic therapy, both within 90 days prior to randomization,
	OR
	  • Within 30 days prior to randomization if the patient has not been hospitalized for HF nor had an urgent HF visit within the past 90 days.

Sex	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	Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol.
Exclusion criteria	Participants are excluded from the study if any of the listed criteria apply.

Medical conditions	• eGFR <25 ml/min/1.73 m^2 at either screening or randomization visit. (Note: one reassessment of eGFR is allowed at the screening and randomization visit, respectively).
	• 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).
	• Acute inflammatory heart disease, e.g. acute myocarditis, within 90 days prior to randomization.
	• Myocardial infarction or any event which could have reduced the ejection fraction within 90 days prior to randomization.
	• Coronary artery bypass graft surgery in the 90 days prior to randomization.
	• Percutaneous coronary intervention in the 30 days prior to randomization.
	• Stroke or transient ischaemic cerebral attack within 90 days prior to randomization.
	• Probable alternative cause of participants' HF symptoms that in the opinion of the investigator primarily accounts for patient's dyspnoea such as significant pulmonary disease, anaemia 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
	  • Haemoglobin <10 g/dl
	  • Valvular heart disease considered by the investigator to be clinically significant
	  • Body mass index >50 kg/m^2 at screening.
	• Systolic blood pressure ≥160 mmHg if not on treatment with ≥3 blood pressure lowering medications or ≥180 mmHg irrespective of treatments on two consecutive measurements at least 2 min apart, at screening or at randomization.
	• 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.
	• Symptomatic hypotension with mean systolic blood pressure <90 mmHg at screening or at randomization.
	• 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.
	• History of peripartum cardiomyopathy, chemotherapy-induced cardiomyopathy, viral myocarditis, right HF in absence of left-sided structural disease, pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy including amyloidosis.

Table 2 (Continued)

	• Presence of left ventricular assist device by the time of screening or randomization. • History of hyperkalaemia or acute renal failure during MRA treatment for >7 consecutive days, leading to permanent discontinuation of the MRA treatment. • 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. • Known hypersensitivity to the study intervention (active substance or excipients). • Hepatic insufficiency classified as Child–Pugh C at screening or randomization. • Addison's disease.
Prior/concomitant therapy	• 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 h prior to randomization. • Participants who require treatment with more than one ACEI, ARB or ARNI, or two simultaneously at randomization. • 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 enrolment into the study. • 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. • Concomitant systemic therapy with potent 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	• 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). • Previous assignment to treatment during this study. • 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. • 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). • 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. • Participant is in custody by order of an authority or a court of law.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BNP, B-type natriuretic peptide; CYP3A4, cytochrome P450 isoenzyme 3A4; eGFR, estimated glomerular filtration rate; HF, heart failure; IV, intravenous; LAA, left atrial area; LAD, left atrial diameter; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Study management and committees

The FINEARTS-HF trial is conducted by Bayer under the guidance of an academic steering committee. An independent external Data Monitoring Committee oversees the trial to ensure participant safety and reviewed results from the interim analyses. A clinical events committee adjudicates all deaths and potential primary non-fatal events according to standardized definitions.

Statistical considerations

The primary analysis will evaluate the total occurrences of the composite of cardiovascular death, hospitalization for HF, and urgent HF events. An intention-to-treat approach will be taken for the primary analysis without accounting for ultimate dose tolerated or treatment continuation in follow-up. The primary analysis of the primary composite endpoint will be based on a Lin, Wei, Yang and Ying (LWYY) model.[23] This is equivalent to the stratified Andersen–Gill model[24] with use of robust standard errors (sandwich estimator) to account for within-participant correlations. The model will include treatment group as a fixed effect and geographic region and baseline LVEF (<60%, ≥60%) as stratification factors. Adjustment will be made to the nominal significance level at the final analysis to take into account the interim analysis (see below).

The trial is designed to show a treatment effect on the primary endpoint with a power of 90% at a two-sided alpha of 5%. The sample size determination is based on a simulation study using a joint frailty model in order to account for the correlation between HF events and cardiovascular death, and to model participant heterogeneity with respect to baseline intensities/hazards.[25] The placebo rate parameter of the Poisson process and the hazard rate of the exponential distribution were initially chosen as 0.014 hospitalizations for HF/month per participant and 0.004 cardiovascular 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 cardiovascular death of 3.5. These observed rates are similar to rates observed in the literature, that is an annualized rate of first composite event of 9.1 was observed in

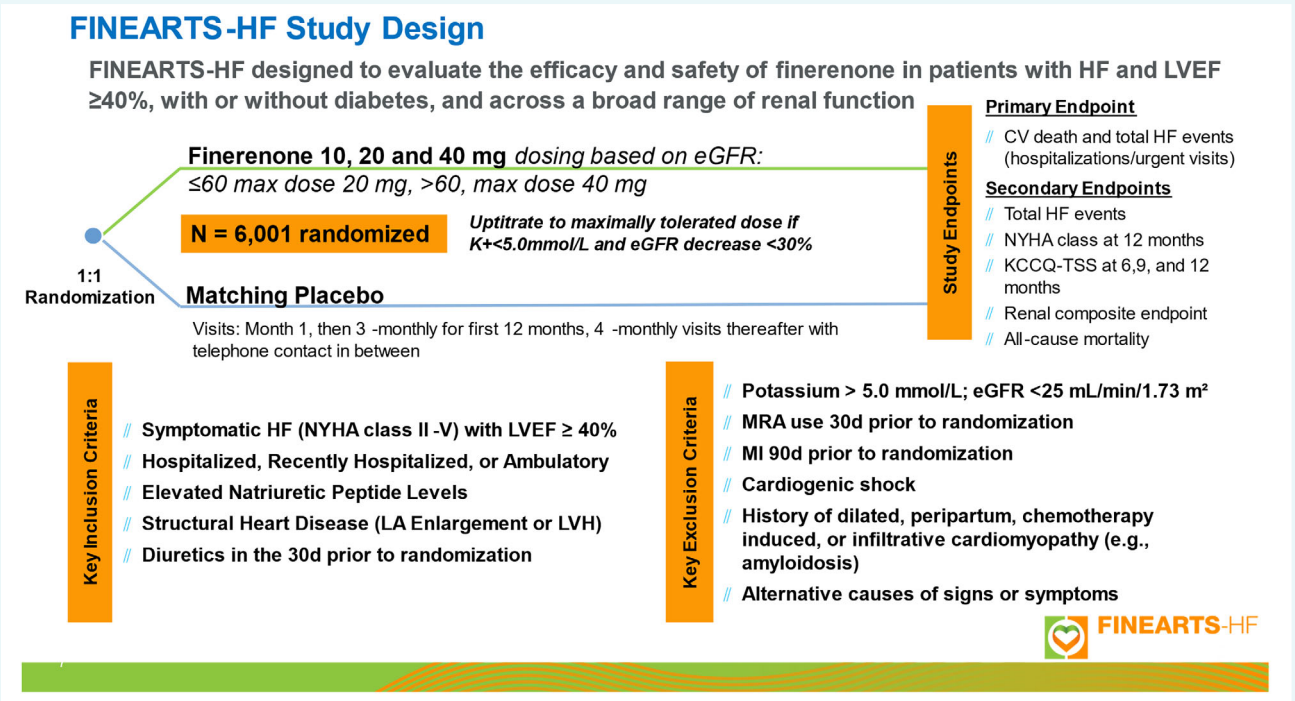

Figure 1 FINEARTS-HF study design. CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; LA, left atrial; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

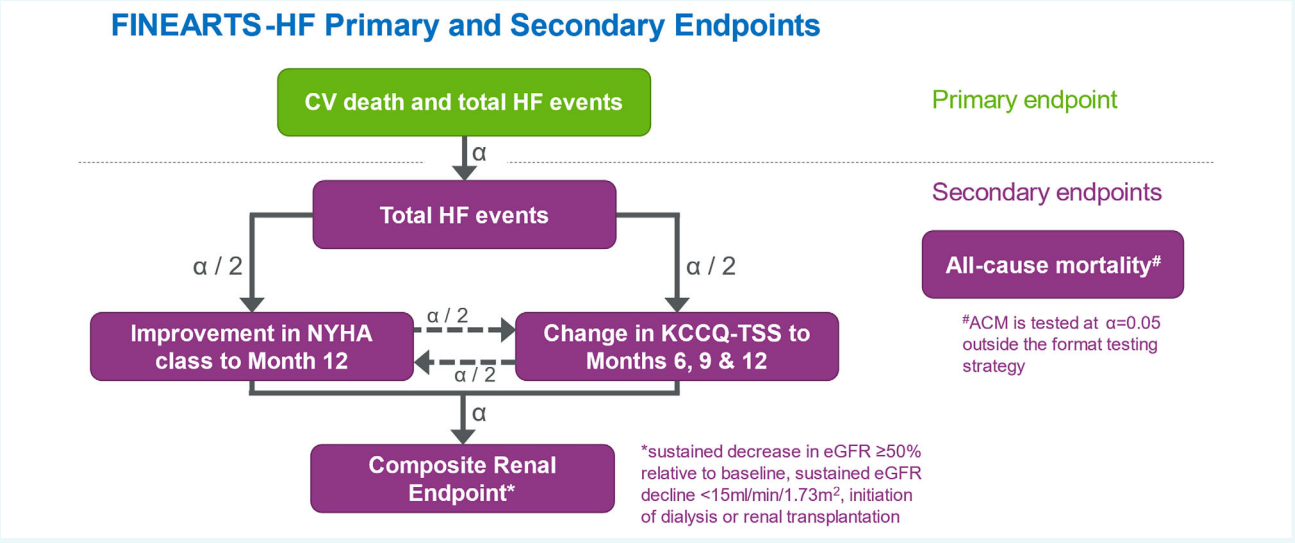

Figure 2 FINEARTS-HF primary and secondary endpoints. ACM, all-cause mortality; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; NYHA, New York Heart Association.

the CHARM-Preserved trial, 8.9 was observed in PARAGON-HF, and 8.5 in the subgroup randomized on the basis of a natriuretic peptide measurement in the TOPCAT trial. Regarding cardiovascular 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 in the TOPCAT natriuretic peptide stratum. Since FINEARTS-HF planned to recruit a higher risk population including more participants with a very recent hospitalization than in previous trials, the rate parameters were subsequently increased by 25% for cardiovascular death leading to a rate of 0.005125 cardiovascular 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.

Based on these calculations, it was originally anticipated that 5500 participants will be randomized. A total of approximately 2375 total (first and recurrent) primary composite events were targeted. Due to blinded event rates being lower than those assumed in the sample size calculation, the planned number of randomized subjects was increased to approximately 6000.

The secondary hypotheses will be formally tested, and statistical inferences will be made only if the primary hypothesis is rejected. Secondary endpoints will be tested sequentially as follows: total HF events, NYHA class and KCCQ (tested using the Bonferroni–Holm procedure), composite renal endpoint. Outside this hierarchy, if the primary hypothesis is rejected, then all-cause mortality will be tested at a full two-sided significance level of 5%.

Total HF events will be analysed using an LWYY model in a similar fashion to the primary endpoint. The percentage of participants with improvement in NYHA class from baseline to month 12, will be analysed with a logistic regression model including factors for treatment group and stratification levels. The absolute change from baseline including measurements up to month 12 of the KCCQ-TSS, will be analysed by a repeated measures mixed model including the factors treatment group, baseline, visit, baseline-by-visit interaction, and factors for the stratification levels. The comparison assumes a common treatment effect across month 6, 9 and 12. The composite renal endpoint and all-cause mortality will be analysed using 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 same stratification factors used for the primary analysis and include treatment group as a fixed effect.

Besides the stratification factors (geographic region and baseline LVEF <60% or ≥60%), key pre-specified subgroups include those defined based on baseline serum potassium, eGFR, atrial fibrillation status, presence or absence of diabetes, and recency of worsening HF event from randomization. Other subgroups of interest are pre-specified in the Regulatory and Academic Statistical Analysis Plans.

Interim analyses

One non-binding interim analysis for futility was planned when approximately 30% of the required total number of primary endpoint events were observed. If the observed rate ratio on the primary endpoint was above 0.95, the trial was planned to be stopped for futility. In addition, one formal interim analysis for efficacy was planned when approximately two-thirds of the required total number of primary endpoint events were observed. If the interim analysis showed clear and consistent benefit in the finerenone treatment group (primary efficacy endpoint with two-sided $p < 0.0027$ and cardiovascular death component with nominal two-sided $p < 0.05$), the Data Monitoring Committee may have recommended early study termination. In both pre-specified interim analyses for futility and efficacy, the Data Monitoring Committee recommended to continue the trial unchanged.

Discussion

FINEARTS-HF will assess the efficacy and safety of the selective non-steroidal MRA finerenone compared to placebo in a broad population of patients with HFmrEF and HFpEF. While MR blockade in this target population has a strong theoretical basis based on pre-clinical data and trials in HFrEF and CKD, the clinical evidence to date has not been definitive. The design of the trial has been informed by learnings from previous large-scale outcome trials of various pharmacotherapies. FINEARTS-HF is large (with over 6000 patients enrolled) and targets a cohort at high risk for disease progression, and thus is well-powered to definitively establish whether non-steroidal MRAs have a role in this patient population. The primary endpoint of the trial will reflect a broader look at 'worsening HF' by including cardiovascular death and total (not just first) HF events. Finally, dosing of finerenone has been optimized and guided by a phase 2 programme[22] in which treatment effects on natriuretic peptide levels appeared to be dose-dependent. FINEARTS-HF will uniquely test a 40 mg target maintenance dose in people with an eGFR >60 ml/min/1.73 m^2, which is not currently available in the treatment of CKD.

In FINEARTS-HF, finerenone will be tested against a placebo comparator as steroidal MRAs currently lack any specific regulatory labelling or class I recommendation for use in patients with HF with mildly reduced or preserved ejection fraction, and thus are not considered a part of global standard of care. We acknowledge however that in the absence of an active-controlled trial (against spironolactone or eplerenone), clinicians may have residual questions about whether finerenone is truly superior to steroidal MRAs that are widely available. Pharmacologically, finerenone is more selective and accumulates less in the kidney, and thus has lower theoretical potential for serious hyperkalaemia than spironolactone.[16] Indeed, a direct head-to-head phase 2 trial in individuals with HFrEF and moderate CKD showed that treatment with finerenone resulted in lower rates of hyperkalaemia, increases in blood potassium levels, and worsening kidney function than spironolactone, although finerenone doses were generally lower than those being tested in FINEARTS-HF.[21] Indirect comparisons with TOPCAT and other ongoing trials of spironolactone in this target population (ClinicalTrials.gov NCT02901184 and NCT04727073) might additionally inform the comparative safety of these therapeutic approaches. In addition to conventional cardiac biomarkers (e.g. natriuretic peptides and troponins), FINEARTS-HF will prospectively collect exploratory biomarkers that relate to its unique mode of action. These biomarker profiles may help to further distinguish finerenone's mechanistic effects compared with those of conventional MRAs.[26,27] Ultimately, FINEARTS-HF is much larger and broader than the previous and ongoing trials investigating spironolactone, and if positive, is best positioned to support a new evidence-based approach in HF with mildly reduced or preserved ejection fraction. Indeed, after FINEARTS-HF, three additional clinical trials are planned under the MOONRAKER programme (that will encompass >15 000 patients in aggregate) to expand evidence generation regarding the definitive role of finerenone across the spectrum of HF.

The trial is also enriched to examine safety and efficacy of finerenone in a number of key subgroups. The trial will have the highest percentage of hospitalized or recently hospitalized patients of any contemporary HFmrEF/HFpEF outcome trials. As global guidelines now support in-hospital and early post-discharge optimization of guideline-directed medical therapies, FINEARTS-HF will directly inform this implementation strategy in the care of

high-risk patients with HFmrEF/HFpEF. As most previous HF trials of steroidal MRAs have enrolled patients in stable ambulatory care, the safety of MRA initiation in this high-risk window of a worsening HF episode is less certain. A previous trial examined the early safety of high-dose spironolactone (administered at 100 mg daily) in 360 patients with acute HF, however MRA therapy was not continued post-discharge in this trial.[28] Rapid implementation of comprehensive guideline-directed medical therapy inclusive of steroidal MRAs in the STRONG-HF trial appeared safe and effective among high-risk patients after hospitalization for HF, however more than two-thirds of participants had HFrEF.[29] Furthermore, FINEARTS-HF is adequately represented across the range of ejection fraction such that the therapeutic effects of non-steroidal MRAs in the >1000 participants with LVEF ≥60% will be clarified.

The study adds data to a better understanding of the role of finerenone across the spectrum of cardio-kidney-metabolic health. To date, large-scale outcome trials of finerenone in CKD have been restricted to those with concomitant diabetes. FINEARTS-HF will be the first outcome trial to test the efficacy and safety of finerenone in patients with and without diabetes and across a broad range of renal function (eGFR down to 25 ml/min/1.73 m^2) and will complement data from the FIND-CKD trial (ClinicalTrials.gov NCT05047263), a dedicated trial of finerenone in patients with CKD without diabetes on change in total eGFR slope. Steroidal MRA use in indicated populations of HF is particularly low in patients with comorbid CKD,[30] so FINEARTS-HF affirming safety of finerenone in this range of kidney function will add confidence to its use at this high-risk intersection. Indeed, a participant-level pooled analysis of FINEARTS-HF, FIDELIO-DKD, and FIGARO-DKD is pre-specified and will help map finerenone's therapeutic effects across cardio-kidney-metabolic disease states.

The FINEARTS-HF trial will determine the efficacy and safety of the non-steroidal MRA finerenone in a broadly inclusive population of hospitalized and ambulatory HF patients with mildly reduced or preserved ejection fraction. FINEARTS-HF has the potential to inform the safe application and implementation of finerenone in this target population.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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References

1. Selye H, Hall CE, Rowley EM. Malignant hypertension produced by treatment with desoxycorticosterone acetate and sodium chloride. *Can Med Assoc J* 1943;**49**:88–92. PMID: 20322846.
2. Agarwal R, Kolkhof P, Bakris G, Bauersachs J, Haller H, Wada T, *et al.* Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. *Eur Heart J* 2021;**42**:152–161. https://doi.org/10.1093/eurheartj/ehaa736
3. Brown JM, Siddiqui M, Calhoun DA, Carey RM, Hopkins PN, Williams GH, *et al.* The unrecognized prevalence of primary aldosteronism: A cross-sectional study. *Ann Intern Med* 2020;**173**:10–20. https://doi.org/10.7326/M20-0065
4. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**:709–717. https://doi.org/10.1056/NEJM199909023411001
5. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, *et al.*; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21. https://doi.org/10.1056/NEJMoa1009492
6. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2024;**26**:5–17. https://doi.org/10.1002/ejhf.3024
7. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* 2022 AHA/ACC/HFSA Guideline for the management of heart failure: Executive summary: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2022;**79**:1757–1780. https://doi.org/10.1016/j.jacc.2021.12.011
8. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, *et al.*; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014;**370**:1383–1392. https://doi.org/10.1056/NEJMoa1313731
9. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, *et al.* Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation* 2015;**131**:34–42. https://doi.org/10.1161/CIRCULATIONAHA.114.013255
10. de Denus S, O'Meara E, Desai AS, Claggett B, Lewis EF, Leclair G, *et al.* Spironolactone metabolites in TOPCAT – new insights into regional variation. *N Engl J Med* 2017;**376**:1690–1692. https://doi.org/10.1056/NEJMc1612601
11. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, *et al.* Medical therapy for heart failure with reduced ejection fraction: The CHAMP-HF registry. *J Am Coll Cardiol* 2018;**72**:351–366. https://doi.org/10.1016/j.jacc.2018.04.070
12. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, *et al.* Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004;**351**:543–551. https://doi.org/10.1056/NEJMoa040135
13. Vardeny O, Claggett B, Vaduganathan M, Beldhuis I, Rouleau J, O'Meara E, *et al.*; TOPCAT Investigators. Influence of age on efficacy and safety of spironolactone in heart failure. *JACC Heart Fail* 2019;**7**:1022–1028. https://doi.org/10.1016/j.jchf.2019.08.019
14. Beldhuis IE, Myhre PL, Claggett B, Damman K, Fang JC, Lewis EF, *et al.* Efficacy and safety of spironolactone in patients with HFpEF and chronic kidney disease. *JACC Heart Fail* 2019;**7**:25–32. https://doi.org/10.1016/j.jchf.2018.10.017
15. Ferreira JP, Pitt B, McMurray JJV, Pocock SJ, Solomon SD, Pfeffer MA, *et al.* Steroidal MRA across the spectrum of renal function: A pooled analysis of RCTs. *JACC Heart Fail* 2022;**10**:842–850. https://doi.org/10.1016/j.jchf.2022.06.010
16. Kolkhof P, Delbeck M, Kretschmer A, SteinkeW, Hartmann E, Barfacker L, *et al.* Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. *J Cardiovasc Pharmacol* 2014;**64**:69–78. https://doi.org/10.1097/FJC.0000000000000091
17. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, *et al.*; FIDELIO-DKD Investigators. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020;**383**:2219–2229. https://doi.org/10.1056/NEJMoa2025845
18. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P, *et al.*; FIGARO-DKD Investigators. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med* 2021;**385**:2252–2263. https://doi.org/10.1056/NEJMoa2110956
19. Agarwal R, Filippatos G, Pitt B, Anker SD, Rossing P, Joseph A, *et al.*; FIDELIO-DKD and FIGARO-DKD Investigators. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: The FIDELITY pooled analysis. *Eur Heart J* 2022;**43**:474–484. https://doi.org/10.1093/eurheartj/ehab777
20. Filippatos G, Anker SD, Agarwal R, Ruilope LM, Rossing P, Bakris GL, *et al.*; FIGARO-DKD Investigators. Finerenone reduces risk of incident heart failure in patients with chronic kidney disease and type 2 diabetes: Analyses from the FIGARO-DKD trial. *Circulation* 2022;**145**:437–447. https://doi.org/10.1161/CIRCULATIONAHA.121.057983
21. Pitt B, Kober L, Ponikowski P, Gheorghiade M, Filippatos G, Krum H, *et al.* Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: A randomized, double-blind trial. *Eur Heart J* 2013;**34**:2453–2463. https://doi.org/10.1093/eurheartj/eht187
22. Filippatos G, Anker SD, Böhm M, Gheorghiade M, Køber L, Krum H, *et al.* A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. *Eur Heart J* 2016;**37**:2105–2114. https://doi.org/10.1093/eurheartj/ehw132
23. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. *J R Stat Soc Series B Stat Methodol* 2000;**62**:711–730. https://doi.org/10.1111/1467-9868.00259
24. Andersen PK, Gill RD. Cox's regression model for counting processes: A large sample study. *Ann Stat* 1982;**10**:1100–1120. https://doi.org/10.1214/aos/1176345976
25. Fritsch A, Schlömer P, Mendolia F, Mütze T, Jahn-Eimermacher A. Efficiency comparison of analysis methods for recurrent event and time-to-first event endpoints in the presence of terminal events – application to clinical trials in chronic heart failure. *Stat Biopharm Res* 2023;**15**:268–279. https://doi.org/10.1080/19466315.2021.1945488
26. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, *et al.*; Aldo-DHF Investigators. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: The Aldo-DHF randomized controlled trial. *JAMA* 2013;**309**:781–791. https://doi.org/10.1001/jama.2013.905
27. Cleland JGF, Ferreira JP, Mariottoni B, Pellicori P, Cuthbert J, Verdonschot JAJ, *et al.* The effect of spironolactone on cardiovascular function and markers of fibrosis in people at increased risk of developing heart failure: The Heart 'OMics' in AGEing (HOMAGE) randomized clinical trial. *Eur Heart J* 2021;**42**:684–696. https://doi.org/10.1093/eurheartj/ehaa758
28. Butler J, Anstrom KJ, Felker GM, Givertz MM, Kalogeropoulos AP, Konstam MA, *et al.*; National Heart Lung and Blood Institute Heart Failure Clinical Research Network. Efficacy and safety of spironolactone in acute heart failure: The ATHENA-HF randomized clinical trial. *JAMA Cardiol* 2017;**2**:950–958. https://doi.org/10.1001/jamacardio.2017.2198
29. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, *et al.* Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): A multinational, open-label, randomised, trial. *Lancet* 2022;**400**:1938–1952. https://doi.org/10.1016/S0140-6736(22)02076-1
30. Patel RB, Fonarow GC, Greene SJ, Zhang S, Alhanti B, DeVore AD, *et al.* Kidney function and outcomes in patients hospitalized with heart failure. *J Am Coll Cardiol* 2021;**78**:330–343. https://doi.org/10.1016/j.jacc.2021.05.002