Academic Statistical Analysis Plan	
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FINEARTS-HF
Academic Statistical Analysis Plan

FINEARTS-HF (FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure)

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 CO-CHAIRS, STEERING COMMITTEE

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1. INTRODUCTION

The FINEARTS-HF trial is a global, multicenter, placebo-controlled, randomized clinical trial investigating the efficacy and safety of the non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone on morbidity and mortality in participants with symptomatic heart failure and left ventricular ejection fraction (LVEF)≥40%. The trial started on September 14, 2020 and has validly randomized 6,001 participants. Approximately 2,375 total (first and recurrent) primary composite events are targeted in this event-driven trial.

The FINEARTS-HF executive committee has developed this academic statistical analysis plan (SAP) that describes pre-specified analyses that are not described in the FINEARTS-HF regulatory SAP or will complement analyses in the regulatory SAP. General principles outlined in the regulatory SAP will be followed unless specified otherwise here. This document is meant to supplement and complement the regulatory SAP and delineate all analyses that were pre-specified prior to database lock.

2. CLINICAL ENDPOINTS OF INTEREST

In addition to the efficacy and safety variables listed in the regulatory SAP, the effect of finerenone on the following endpoints will be explored. These events that are imbalanced between arms may be analyzed as time-to-event to better understand the time course of event accrual.

- An expanded composite outcome of CV death and worsening HF event (defined more broadly as inclusive of outpatient worsening HF events initiation or intensification of oral therapy for HF)
- Composite of HF-related death and worsening HF events
- Cardio-renal composite endpoint which includes components of the primary endpoint and components of the prespecified secondary renal endpoint.
- Hierarchical composite endpoint specifically examining the renal composite endpoint and cardiorenal composite endpoints analyzed using win statistics (hierarchies to be defined before analysis)
- Achievement of post-randomization blood pressure control in those with blood pressure above established thresholds at baseline, including those with apparent treatment resistant hypertension (definition to be defined prior to analysis)
- Changes in pulse pressure and heart rate
- First and total investigator-reported fatal or non-fatal myocardial infarction
- First and total investigator-reported fatal or non-fatal stroke
- Cardiac ischemic events including myocardial infarction, unstable angina, and unplanned coronary revascularization (individually and as a composite)
- Major adverse cardiac events defined either as i) a composite of CV death, non-fatal myocardial infarction, or non-fatal stroke or ii) a composite of death from atherosclerotic CV disease, non-fatal myocardial infarction, or non-fatal stroke
- Proportion of patients with clinically meaningful deterioration (5 point or greater worsening), and small (≥5 point), moderate (≥10 point) and large (≥20 point) improvement in KCCQ-TSS is prespecified in the regulatory SAP. Similar responder analyses will be performed for KCCQ-CSS, OSS, PL, QoL and Social Limitations Scores.
- Analysis of individual domains and questions of the KCCQ
- In addition to assessing improvement in NYHA class as prespecified in the regulatory SAP, changes in NYHA class will be analyzed on an ordinal basis
- Proportion of patients who become NYHA functional class I post-randomization
- Analysis of days alive and out of hospital, days lost due to death or hospitalization adjusted for quality of life using KCCQ-OSS, EQ-5D-5L, and NYHA, and “home time”
- Outcomes related to new onset AF/AFL and total number of episodes of AF/AFL
- Ventricular arrhythmias, defibrillator discharges, resuscitated cardiac arrest, or sudden death
- Post-randomization HF hospitalizations based on treatment complexity (e.g., standard intravenous diuretics, other intravenous HF therapies, mechanical fluid removal, invasive or non-invasive ventilation, mechanical circulatory support) and treatment course (e.g., intensive care unit requirement, length of stay)
- Outcomes related to COVID-19, pneumonia, or other infections occurring during the trial

- Post-randomization changes in medications:
    - New initiation, discontinuation, or dose changes of diuretics
    - New initiation, discontinuation, or dose changes of ACE inhibitor / ARB / ARNI
    - New initiation or discontinuation of SGLT2 inhibitors
    - New initiation of ivabradine
    - New initiation of vericiguat
    - New initiation of hydralazine (+/- nitrates)
    - Implantation of pacemaker, CRT-P/D and ICD
    - New initiation or discontinuation of potassium lowering therapies
    - New initiation or discontinuation of potassium supplementation
    - Post-randomization open-label use and dosing of mineralocorticoid receptor antagonists (including spironolactone, eplerenone, potassium canrenoate, finerenone)
    - Post-randomization changes in number of blood pressure lowering therapies
    - In the T2D subgroup, new anti-hyperglycemic therapy initiation and discontinuation and changes in insulin dose (in those on insulin at baseline) will be examined

3. LABORATORY-BASED ENDPOINTS OF INTEREST

The effect of finerenone will be evaluated for all laboratory measures of interest using each as a continuous variable. The following laboratory-based endpoints will be assessed in addition to the analyses described in the regulatory SAP:

- eGFR
  - The composite renal endpoint as a secondary endpoint is defined as sustained decrease in eGFR ≥50% relative to baseline over at least 4 weeks, or sustained eGFR decline <15ml/min/1.73m2 or initiation of dialysis or renal transplantation. The regulatory SAP prespecifies analyses of sustained declines in eGFR declines reaching ≥50% and ≥57% thresholds from baseline. Lower thresholds (≥30% and ≥40%) for sustained decreases in eGFR will be considered. In addition, a blanking period will be included to account for acute, expected eGFR changes. The renal composite endpoint will further be evaluated with and without inclusion of renal and cardiovascular death.
  - Between arm differences in total, acute, chronic slopes will be estimated
  - "Unconfounded" slope analyses will additionally be performed examining the eGFR changes from randomization to the measurement off treatment
  - Focused examination of the "eGFR dip", the acute changes in eGFR at 1-month and 3-months after randomization, including assessment of the prognostic association between these early changes in eGFR and subsequent cardiovascular and kidney outcomes
  - Recalculation of eGFR based on variable calculators (including the 2009 and 2021 CKD-EPI Equations)
  - Changes in KDIGO risk categories and transitions in CKD stages post-randomization. This will be separately examined overall and in subgroups with and without diabetes.
  - In patients without CKD at baseline, prevention of CKD will be separately assessed (defined based on eGFR falling below 60mL/min/1.73m^2 or new-onset micro or macro-albuminuria).
- UACR
  - New-onset macroalbuminuria (among those with normoalbuminuria or microalbuminuria at baseline) or microalbuminuria (among those with normoalbuminuria at baseline)
  - Regression to normoalbuminuria (from both micro- and macroalbuminuria at baseline) or microalbuminuria (among those with macroalbuminuria at baseline)
- Other renal biomarkers
  - Other biomarkers reflecting kidney function (e.g. cystatin C) or glomerular or tubular injury or predict kidney disease (e.g. urine adenine) that may be measured in biobanked samples after trial completion
- Metabolic biomarkers
  - Changes in hemoglobin A1c will be examined in the overall population and changes in hemoglobin A1c and blood glucose in patients with diabetes and prediabetes (see Special Populations). Other metabolic biomarkers that may be measured in biobanked samples after completion of the trial (e.g. autoantibodies for detection of T1D)
- Potassium

  - New onset hypokalemia (<3.5 mmol/L)
  - Assessment of mortality and cardiovascular events for any given potassium level in both arms
- Sodium
  - Development of hypo- and hyper-natremia during follow up and resolution of hypo- and hyper-natremia during follow-up. Effect of treatment on sodium as a continuous variable will additionally be examined, as will the association between baseline levels (categories, continuous) and clinical outcomes.
- Chloride
  - Development of hypo- and hyper-chloremia during follow up and resolution of hypo- and hyper-chloremia during follow-up. Effect of treatment on chloride as a continuous variable will additionally be examined, as will the association between baseline levels (categories, continuous) and clinical outcomes.
- Uric acid
  - Change in uric acid level with finerenone treatment and incidence of gout. Association between uric acid level at baseline (categories, continuous) and clinical outcomes.
- Hematologic biomarkers
  - Change in hemoglobin and hematocrit with finerenone treatment and incidence of anemia/resolution of anemia. Association between hemoglobin and hematocrit levels at baseline (categories, continuous), and anemia, and clinical outcomes.
  - Change in neutrophil/lymphocyte ratio with finerenone treatment. Association between neutrophil/lymphocyte ratio at baseline (categories, continuous) and clinical outcomes.
- Cardiac biomarkers
  - Changes in NT-proBNP at 3 months and 12 months and proportion of patients with NT-proBNP levels <1,000 pg/mL post-randomization
  - Changes in high-sensitivity troponin at 3 months and 12 months and proportion of patients with levels in the normal reference range post-randomization
  - Other cardiac biomarkers (e.g. markers of extracellular matrix turnover) that may be measured in biobanked samples after completion of the trial
- Renin and aldosterone levels
  - Change in renin and aldosterone levels and aldosterone renin ratio with finerenone treatment
  - Association between renin and aldosterone levels and aldosterone renin ratio at baseline and clinical outcomes
  - Assessment of proportion of patients with evidence of primary hyperaldosteronism based on renin and aldosterone levels
- Other biomarkers will be analyzed at baseline, month 3, month 12, and during the end of study visit. Finerenone's treatment effects on these biomarkers over time and the association between these biomarkers at baseline (categories, continuous) will be assessed.
  - Biomarkers of fibrosis including but not limited to N-terminal propeptide of collagen I and III, tissue inhibitor of matrix metalloproteinase 1, carboxyl-terminal telopeptide of collagen type I, and soluble ST2
  - Growth/differentiation factor-15
  - Cancer antigen 125
  - High sensitivity C-reactive protein

4. BREAKDOWN OF ENDPOINTS

- Mode of death (including sudden death, worsening HF death, other CV death, non-CV deaths)
- First and total all-cause hospitalizations, CV hospitalizations, and reasons for hospitalization (non-CV hospitalization, HF-related hospitalization, and other CV hospitalizations)
- Breakdown of worsening HF events (including urgent visits / Emergency Department stays / oral loop diuretic escalation)
- The primary endpoint of CV death and total HF events and the endpoint of CV death alone will be considered with and without incorporation of unknown / undetermined deaths. In a prespecified exploratory analysis, we will apply a probabilistic model (predetermined prior to database lock) to better distinguish unknown deaths as either CV or non-CV in etiology. This probabilistic model will be built based on known clinical factors that differentially predict adjudicated known cases of CV vs. non-CV deaths.

5. SPECIAL POPULATIONS

- **Recent Worsening HF Event:** FINEARTS-HF is specifically enriched to examine the population of patients with recent worsening HF. Depending on the analysis, subpopulations of interest may be considered including randomization at the time of a hospitalization for HF or urgent HF visit, within 7 days of worsening HF, and within 3 months of worsening HF.
    - Among those who are hospitalized at the time of randomization, 30-, 60-, and 90-day readmissions (all-cause, HF-related, and CV-related) will be examined
    - Early changes in diuretic use and dosing
    - Early trajectory of health status and quality of life
    - Early safety and tolerability with particular attention to blood pressure and renal function changes
- **Diabetes Status:** As finerenone was previously studied in patients with chronic kidney disease exclusively *with* comorbid diabetes, FINEARTS-HF will provide the largest examination to date regarding the use of finerenone in patients *without* diabetes, as well as with prediabetes.
    - Treatment effects on primary and secondary endpoints will be assessed by glycemic categories (no diabetes, prediabetes, and T2D), across HbA1c as a continuous measure (in above categories and in the normal range), and across various background anti-hyperglycemic therapies including insulin
    - In the T2D subgroup, new anti-hyperglycemic therapy initiation and changes in insulin dose (in those on insulin at baseline) will be examined
    - In the T2D subgroup, changes in hemoglobin A1c, including measures of glycemic stability/variability, will be examined
    - In the T2D subgroup, duration of diabetes will be examined
    - In the T2D subgroup, evaluation based on subgroups defined by complications of diabetes (such as neuropathy or retinopathy)
    - In the T2D subgroup, assessment of the primary and secondary endpoints will be performed by background anti-hyperglycemic therapies including focused examination of patients on various combinations of therapies
    - In the T1D subgroup, changes in NT-proBNP and changes in high-sensitivity troponin at baseline, at 3 months and 12 months at 3 months and 12 months will be examined
    - In the diabetic subgroup, initiation of anti-VEGF therapy or laser eye treatment
    - In the diabetic subgroup, assessment of adverse event difference of diabetic retinopathy adverse events & new onset of diabetic retinopathy (by adverse events).
    - In the non-T2D subgroup, new diagnosis of diabetes will be examined (from without diabetes and from prediabetes at baseline)
    - Focused assessment of the renal endpoints as described in both the regulatory and academic SAPs will be performed separately in patients with and without diabetes
    - Focused assessment of safety and tolerability as described in the regulatory SAP will be performed separately in patients with and without diabetes

6. SUBGROUPS

In addition to the subgroups listed in the regulatory SAP, the following subgroups of interest will be explored to examine event rates and for consistency of efficacy and safety of finerenone. All subgroups will be identified based on randomization or pre-randomization data unless otherwise specified. For each subgroup, we will assess the treatment effect and interaction with treatment for the primary endpoint, each of the secondary endpoints, components of the primary endpoint, safety endpoints, as well additional endpoints of interest. For laboratory variables, the association between baseline levels and outcomes will be evaluated, along with the effect of finerenone on these variables.

- Potassium subgroups in the regulatory SAP are specified according to the following cutpoints (≤4.5, >4.5 mmol/L). Additional subgroups defined by median, quantiles, and other standard definitions of hypo-, hyper- and normo-kalemia will be assessed. Potassium will additionally be examined as a continuous function.
- Sodium subgroups defined by the median, quantiles, and standard definitions of hypo-, hyper- and normo-natremia. Sodium will additionally be examined as a continuous function.
- Chloride subgroups defined by the median, quantiles, and standard definitions of hypo-, hyper- and normo-chloremia. Chloride will additionally be examined as a continuous function.
- Hemoglobin and hematocrit subgroups defined by the median, quantiles, and standard definitions of anemia. Hemoglobin and hematocrit will additionally be examined as a continuous function.
- eGFR subgroups in the regulatory SAP are specified according to the following cutpoints (eGFR <60, ≥60 mL/min/1.73 m²). eGFR categories will additionally be evaluated according to different cutoffs (eGFR 25 to <45, 45 to <60, ≥60 mL/min/1.73 m²), the full KDIGO risk categories, and treatment effects will be examined across eGFR as a continuous function
- Focused examination of Stage 4 CKD (if eGFR was less than 30mL/min/1.73m^2 at randomization or at any post-randomization measurement). Covariate adjustment will be employed as needed to address potential between arm differences that were introduced post-randomization.
- UACR subgroups in the regulatory SAP are specified according to the following cutpoints (<30 vs. ≥30 mg/g and ≥ 300mg/g). UACR will additionally as a continuous function.
- BUN and BUN/creatinine ratio subgroups defined by the median and quantiles.
- BUN and BUN/Cr ratio will additionally be examined as a continuous function.
- Patients suspected to have primary hyperaldosteronism based on renin and aldosterone levels
- BMI subgroups in the regulatory SAP are specified according to the following cutpoints (30kg/m^2). BMI categories will additionally be evaluated according to the full WHO classification and treatment effects will be examined across BMI as a continuous function. Similar analyses will be used for other recognized anthropometric measures e.g., waist-to-height ratio, waist-hip ratio, body roundness index, examining these as categorical variables using recognized cut

points, medians, quantiles, and as continuous variables. Ethnicity-appropriate thresholds for obesity definitions will also be applied in separate analyses.

- Subgroups defined by standard nutritional indices e.g., the geriatric nutritional risk index (GNRI), prognostic nutritional index (PNI), and controlling nutritional status (CONUT), examining these as categorical variables using recognized cut points, medians, quantiles, and as continuous variables.
- Age subgroups in the regulatory SAP are specified according to the following cutpoints (median age). Specific evaluation of older age categories will be considered and treatment effects will be examined across age as a continuous function
- Race and ethnicity subgroups are specified in the regulatory SAP. Focused examination of patients who are Black, Asian, Native American, and Hispanic/Latinx populations.
- Systolic blood pressure subgroups in the regulatory SAP are specified according to the following cutpoints (median SBP). SBP and DBP will be assessed at the median, quantiles, and various global definitions of hypertension (based on both SBP and DBP). Treatment effects will be examined across SBP and DBP as a continuous function
- Pulse pressure will be assessed at the median, quantiles. Treatment effects will be examined across categories as a continuous function
- Heart rate will be assessed at the median, quantiles. Treatment effects will be examined across categories as a continuous function. Separate analyses will be conducted overall and in patients with and without AF/AFL.
- Patients with apparent treatment resistant hypertension (definition to be determined prior to analysis)
- Atrial fibrillation on baseline ECG is a prespecified subgroup in the regulatory SAP. Atrial fibrillation or atrial flutter on baseline ECG will be further examined. In addition, a previous history of atrial fibrillation/flutter will be assessed, together with the overlap between medical history and baseline ECG and derived history of persistent/permanent AF versus paroxysmal AF. Additional analyses will be conducted examining rhythm across baseline heart rate categories.
- Patients with improved/recovered LVEF (those who had LVEF ≤40% at any time prior to randomization)
- LVEF is a stratification variable in the regulatory SAP at the following cutpoint (<60%, ≥60%). Different cutpoints (≤ 49%, 50 to 59%, ≥60%) will also be applied to examine those with HF with mildly reduced ejection fraction. Additional LVEF subgroups to limit digit preference will be considered and treatment effects will be examined across LVEF as a continuous function. In addition, the two-way interaction between sex and LVEF will be examined.
- Other anthropometric indices e.g., waist-to-hip ratio, waist-to-height ratio using quantiles and recognized cutpoints
- Time from prior HF hospitalization (never hospitalized, randomization during hospitalization or within 7 days, 3 months, 6 months, 9 months, 12 months, or 2 years of prior hospitalization)
- Time from index HF diagnosis, analyzed as both a continuous and a categorical variable
- Patients with COPD, asthma or both

- Patients with OSA
- Patients with history of current or former smoking and degree of alcohol consumption (if any)
- Patients with cirrhosis
- Patients with metabolic dysfunction–associated fatty liver disease or metabolic dysfunction-associated steatohepatitis
- Patients who develop COVID-19 or other infections in follow-up
- Patients with any atherosclerotic cardiovascular disease
- Patients with history of stroke/TIA
- Patients with history of coronary artery disease / prior MI
- Patients with history of coronary artery bypass graft surgery
- Patients with peripheral artery disease
- Patients with metabolic syndrome (using standard definitions)
- Subgroups based on baseline use and dosing of diuretics
- Patients with multimorbidity and frailty
- Patients with cardio-kidney-metabolic overlap (intersection of atherosclerotic cardiovascular disease, CKD, and diabetes). CKM overlap will be evaluated based on number of CKM conditions (0, 1, 2, or 3) and based on the type of overlap.
- Total baseline medications will be categorized as ("non-polypharmacy": <5 medications; "polypharmacy": 5 to 9 medications; and "hyperpolypharmacy": ≥10 medications) and also assessed as a continuous function
- Number of blood pressure lowering therapies at baseline as well as up/down titration of blood pressure lowering therapies during the trial
- Patients with baseline risk as determined by the MAGGIC and other HF risk scores
- Patients with baseline kidney risk as determined by the Kidney Failure Risk Equation, Klinrisk, and KDIGO risk categories
- Subgroups based on baseline evidence of congestion and congestion scores
- QRS duration on ECG and bundle branch block
- Regional subgroups based on socioeconomic differences (assessed by the GINI coefficient). In addition to the regional grouping specified in the regulatory SAP, alternative group will be considered depending on representation and number of events of interest and to ensure consistency with adjacent trial programs (for pooling purposes).
- Subgroups based on KCCQ-TSS and other KCCQ domains at baseline.
- Subgroups based on EQ-5D-5L VAS and index scores at baseline.
- NT-proBNP and high-sensitivity troponin will be examined at median, quantiles, and as continuous measures
- Patients with a pacemaker, ICD, and/or CRT device
- Patients with phenotypic characteristics of amyloid cardiomyopathy, based on validated clinical models/scores
- Patients with left ventricular hypertrophy, including asymmetric patterns based on qualifying site-reported echocardiographic data
- Patients with left atrial enlargement based on qualifying site-reported echocardiographic data

- Medication based subgroups:
  - Use and dosing of diuretics, including separate evaluation of loop diuretics alone and combination diuretic therapies (loop plus non-loop diuretic)
  - History of any prior MRA use prior to randomization
  - Patients on or off ACE inhibitors, ARBs, or ARNI at baseline
  - Patients on or off an SGLT2 inhibitor
  - Patients on or off a GLP-1 receptor agonist
  - Patients on or off β-blockers at baseline
  - Patients on or off potassium supplements at baseline
  - Patients on or off potassium lowering therapies at baseline
  - Patients on or off statin therapy
  - Number of blood pressure lowering therapies at baseline
  - Background HF therapies including focused examination of patients on various combinations of therapies (including the Heart Failure Collaboratory score)

7. ALTERNATIVE ANALYTIC APPROACHES

Unless otherwise specified, these alternative approaches will be considered for the primary endpoint and each of the secondary endpoints.

- Win statistics (win ratio, win odds, and net benefit) using different clinically relevant hierarchies e.g., death, heart failure hospitalization, urgent heart failure visit requiring IV therapy, outpatient therapy for worsening HF, quality of life, and kidney endpoints
- Win statistics to assess net clinical benefit assessment in balancing efficacy and safety/adverse events (this may include hyperkalemia, worsening renal function, and/or hypotension)
- Win statistics evaluating various novel kidney hierarchical composite renal endpoints, incorporating various thresholds of sustained eGFR decreases, ESKD, renal death, and eGFR slope. Additional analyses will incorporate cardiovascular and all-cause death in the hierarchy.
- Recurrent events (first and repeat hospitalizations for heart failure and worsening HF events) analyzed using multiple approaches including the LWYY and joint frailty models, Prentice, Williams, and Peterson (PWP) total time and gap time models
- Model-free area under the curve (AUC) approach to efficacy analyses. Cumulative event curves (based on Nelson-Aalen or the Ghosh-Lin methods) will be constructed for recurrent events. The integrated AUC, representing the mean total time lose due to recurrent HF events and CV death, will be estimated by treatment arm. The absolute difference and relative ratio of the resulting AUCs will then be estimated.
- Area under the curve (RMST methods) application to first primary and secondary endpoints
- Time-varying treatment effect will examine potential hazard ratio drift or violations in the proportional hazards assumption for time to first endpoints
- Multi-state modeling of changes in transitional states (ranging from alive and well to death)
- Time to onset of benefit of finerenone for primary endpoint is prespecified in the regulatory SAP. Additional analyses will be performed to evaluate first nominal statistical significance and first sustained statistical significance for all primary and secondary endpoints that reached statistical significance by the end of the trial
- Forecasting lifetime benefit of finerenone if treatment effects were assumed to be maintained long-term
- Absolute risk reductions and NNT calculation overall and across key subgroups
- Cost effectiveness based on US perspective, European perspective, and Other Regions of the World perspective
- Assessment of FINEARTS-HF trial and potential label eligibility in the GWTG-HF registry and other “real-world” datasets
- “Real world” application of the FINEARTS-HF trial findings to the GWTG-HF registry and other datasets to estimate projected benefit if finerenone was implemented in usual care
- Clinical assessment of patients in the 30-days post-treatment after the end of the randomized period
- Determination if treatment effects of finerenone on primary and secondary endpoints persistent even among those who experience interval safety events (such as hypotension, worsening renal function, hyperkalemia). This will specifically also examine treatment

effects in those who experience a decline in eGFR during the trial to levels below that required for initial trial eligibility.

- Estimation of treatment effects on primary and secondary outcomes by dose achieved (adjusted according to the maximum dose allowed per protocol by baseline eGFR), including with assessment of dose as a time-varying covariate and as average dose used during trial follow-up
- Comparison of established prognostic risk models (e.g. MAGGIC, PREDICT-HF, EMPEROR-Preserved) to predict outcomes
- Assessment of heterogeneity of risk
- Geographic region is a stratification variable in the regulatory SAP, but further stratification by country and site will be examined.
- PGIC and PGIS are being used as an anchor to estimate clinically meaningful change in KCCQ-TSS as specified in the regulatory SAP. We will carry out similar analyses for other KCCQ domains/summary scores including KCCQ-CSS, OSS, PL, QoL and Social Limitations Scores.
- Mediation analyses examining various early biomarkers as discussed in Section 3 and influence on treatment effects of finerenone.
- Multivariable interaction model examining heterogeneity in treatment effects simultaneously including all interaction terms for key subgroups (to be defined prior to analysis)
- Association between time-varying maximum potassium level with finerenone (when compared with a referent participant on placebo who never experienced potassium levels ≥5.0 mEq/L) and hazard of key clinical outcomes. Models will be adjusted for age, eGFR, baseline potassium, and diabetes mellitus.
- Association of finerenone use with readmission within 30-, 60-, and 90 days after a post-randomization hospitalization for HF
- Comparison of investigator reported vs. CEC-adjudicated endpoints (including by individual reviewers) vs. those captured by natural language processing of the site-reported event dossiers. Comparisons will be summarized as raw agreement and kappa statistic; sensitivity, specificity, positive predictive value, negative predictive value. Treatment effect of finerenone vs. placebo will be assessed across each event defined as investigator reported, CEC-adjudicated, or NLP-captured. The NLP models would include the C3PO model, the INVESTED model, and the C3PO + INVESTED model.
- Re-analysis of FINEARTS-HF based on Bayesian methods incorporating non-informative and various informative prior distributions based on the totality of accumulated evidence from adjacent disease states (such as CKD), the phase II finerenone program, and other trials investigating MRAs in heart failure.
- Incidence and predictors of hyperkalemia during follow-up, including development of a hyperkalemia risk score and analysis of risk based on potassium levels as a time-varying covariate
- Indirect comparison of FINEARTS-HF and TOPCAT by applying inverse probability weighting to “match” the patient populations. Focused examination of participants enrolled in FINEARTS-HF Americas will be compared with those enrolled in TOPCAT Americas. Clinical events, safety events, and blood pressure changes will be indirectly compared between trial programs.
- Bidirectional association between incident kidney outcomes and risk of subsequent cardiovascular events, and vice versa

- Association between UACR and cardio-kidney outcomes, overall and stratified by CKD stage (based on eGFR). The comparative prognostic significance of UACR vs. eGFR on cardio-kidney outcomes will be further tested.

8. POOLED ANALYSES

Separate SAPs will be developed to detail planned analyses in the combined datasets of the following clinical trials:

- FINEARTS-HF + FIDELITY program (which included FIGARO-DKD NCT02545049 and FIDELIO-DKD NCT02540993)
- FINEARTS-HF + subgroup of patients with HF in the FIDELITY program (which included FIGARO-DKD NCT02545049 and FIDELIO-DKD NCT02540993)
- FINEARTS-HF + FIND-CKD (NCT05047263)
- FINEARTS-HF + FIND-CKD (NCT05047263) + FIDELITY program (which included FIGARO-DKD NCT02545049 and FIDELIO-DKD NCT02540993)
- FINEARTS-HF + subgroup of patients with HF in FIND-CKD (NCT05047263) + + subgroup of patients with HF in the FIDELITY program (which included FIGARO-DKD NCT02545049 and FIDELIO-DKD NCT02540993)
- FINEARTS-HF + REDEFINE-HF
- FINEARTS-HF + REDEFINE-HF + FIDELITY program (which included FIGARO-DKD NCT02545049 and FIDELIO-DKD NCT02540993)
- FINEARTS-HF + REDEFINE-HF + subgroup of patients with HF in the FIDELITY program (which included FIGARO-DKD NCT02545049 and FIDELIO-DKD NCT02540993)
- FINEARTS-HF + REDEFINE-HF + FIND-CKD (NCT05047263) + FIDELITY program (which included FIGARO-DKD NCT02545049 and FIDELIO-DKD NCT02540993)
- FINEARTS-HF + REDEFINE-HF + subgroup of patients with HF in FIND-CKD (NCT05047263) + subgroup of patients with HF in the FIDELITY program (which included FIGARO-DKD NCT02545049 and FIDELIO-DKD NCT02540993)
- FINEARTS-HF + FINALITY
- FINEARTS-HF + FINALITY + FIDELITY program (which included FIGARO-DKD NCT02545049 and FIDELIO-DKD NCT02540993)
- FINEARTS-HF + FINALITY + FIND-CKD (NCT05047263) + FIDELITY program (which included FIGARO-DKD NCT02545049 and FIDELIO-DKD NCT02540993)
- FINEARTS-HF + FINALITY + subgroup of patients with HF in FIND-CKD (NCT05047263) + subgroup of patients with HF in the FIDELITY program (which included FIGARO-DKD NCT02545049 and FIDELIO-DKD NCT02540993)
- FINEARTS-HF + REDEFINE-HF + FINALITY
- FINEARTS-HF + REDEFINE-HF + FINALITY + FIDELITY program (which included FIGARO-DKD NCT02545049 and FIDELIO-DKD NCT02540993)
- FINEARTS-HF + REDEFINE-HF + FINALITY + subgroup of patients with HF in the FIDELITY program (which included FIGARO-DKD NCT02545049 and FIDELIO-DKD NCT02540993)
- FINEARTS-HF + REDEFINE-HF + FINALITY + FIND-CKD (NCT05047263) + FIDELITY program (which included FIGARO-DKD NCT02545049 and FIDELIO-DKD NCT02540993)
- FINEARTS-HF + REDEFINE-HF + FINALITY + subgroup of patients with HF in FIND-CKD (NCT05047263) + subgroup of patients with HF in the FIDELITY program (which included FIGARO-DKD NCT02545049 and FIDELIO-DKD NCT02540993)

FINEARTS ACADEMIC SAP

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