

Finerenone in Patients with Heart Failure with Mildly Reduced or Preserved Ejection

Fraction: Rationale and Design of the FINEARTS-HF Trial

Supplemental Appendix

Dosage of Study Intervention for Administration	Pg.2
Protocol Suggested Management and Dosing	Pg.4
Adjustments in Response to Changes in Renal Function	
Eligibility Flowchart	Pg. 6
Protocol Amendment Summary of Changes Table	Pg. 7

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Dosage of Study Intervention for Administration

eGFR value at the Baseline Visit, based on local laboratory results:	eGFR 25 to ≤60 mL/min/1.73m	eGFR >60 mL/min/1.73m ²
<p>Participant randomized to group:</p> <p>Starting dose:</p> <p>Maintenance dose:</p> <p>Minimum dose after down-titration:</p> <p>Maximum dose after up-titration:</p>	<p><u>Finerenone</u> <u>Placebo</u></p> <p>10 mg finerenone OD Placebo OD (Dose Level 1)</p> <p>20 mg finerenone OD Placebo OD (Dose Level 2)</p> <p>10 mg finerenone OD Placebo OD 20 mg finerenone OD Placebo OD</p>	<p><u>Finerenone</u> <u>Placebo</u></p> <p>20 mg finerenone OD Placebo OD (Dose Level 2)</p> <p>40 mg finerenone OD Placebo OD (Dose Level 3)</p> <p>10 mg finerenone OD Placebo OD 40 mg finerenone OD Placebo OD</p>
Study intervention intake	<p>One tablet of study intervention OD, preferably in the morning at approximately the same time each day.</p> <p>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</p>	
Missed intake	<ul style="list-style-type: none"> • 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	<p><u>Finerenone</u></p> <ul style="list-style-type: none"> • 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. <p><u>Placebo</u></p> <ul style="list-style-type: none"> • Sham-titrate. 	

Down-titration of dose

- 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.

Protocol Suggested Management and Dosing Adjustments in Response to Changes in Potassium and Renal Function

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
≥6.0	Interrupt study intervention and K ⁺ should be re-checked within 72 h of initial K ⁺ result awareness
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:

- If the participant is already on dose level 1 no further decrease is possible after interruption, the same dose level should be restarted 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.
- 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.
- In case of hyperkalemia, it is at the investigator's discretion to take measures, including treatment and monitoring in accordance with local practice standards,

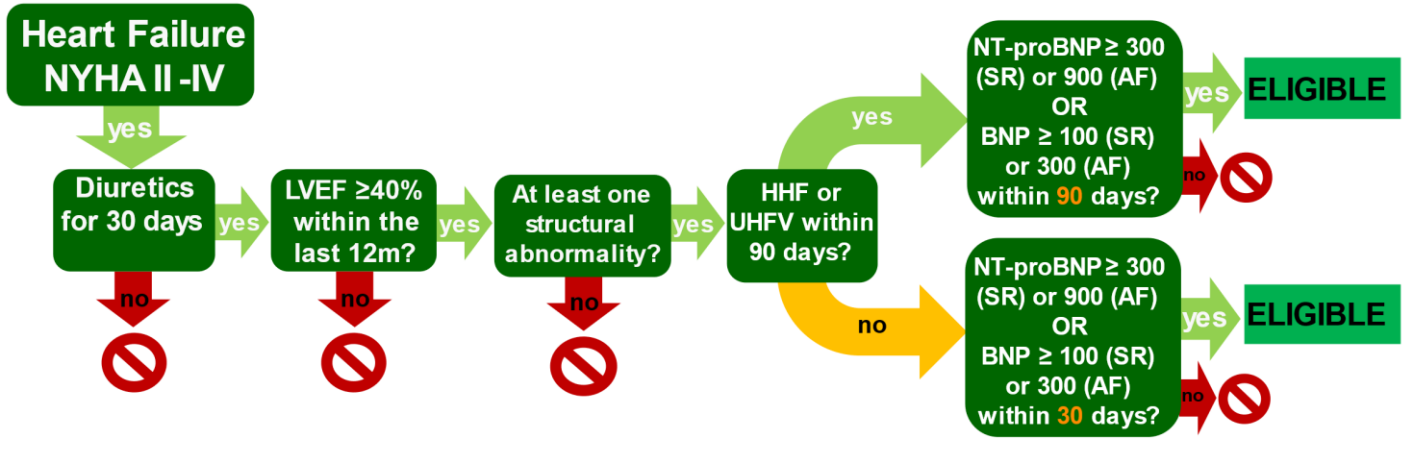
Protocol Suggested Management and Dosing Adjustments in Response to Changes in Potassium and Renal Function

eGFR (mL/min/1.73 m ²) at any time after randomization	Action to be taken
Decrease $\geq 25\%$ and $< 40\%$ from baseline	<ul style="list-style-type: none"> • Check for potential reversible causes: <ul style="list-style-type: none"> • Concomitant medications known to affect renal function (e.g. NSAIDs, antibiotics) • Adverse event (e.g. urinary infection, urinary retention, dehydration) • Address potential reversible causes if considered clinically appropriate
Decrease $\geq 40\%$ from baseline	<ul style="list-style-type: none"> • Check for potential reversible causes and address, as above. • At the investigator's discretion, study drug can be down-titrated or interrupted as follows: <ul style="list-style-type: none"> • 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). • Re-test at central laboratory after 4 weeks to confirm eGFR decrease of $\geq 50\%$ or $\geq 57\%*$

Abbreviations: eGFR = estimated glomerular filtration rate; NSAID = non-steroidal anti-inflammatory drug

* Decrease based on central laboratory data.

Eligibility Flowchart



HHF: hospitalization for heart failure
 UHFV: urgent heart failure visit
 SR: sinus rhythm
 AF: atrial fibrillation

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	Details of MRA and its effects adjusted.	current status of
Section 7.1 Discontinuation of Study Intervention	Addition of maximum permissible duration 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 $\geq 57\%$ 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	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> -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> $\geq 50\%$ <u>or</u> $\geq 57\%$	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 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 in the document that are not listed in this table.