STATISTICAL ANALYSIS PLAN

Effects of Finerenone on Renal Hemodynamics and Oxidative Stress

Investigational products: Finerenone

Study code: Fine

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Short title: Finerenone and renal oxidative stress

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List of abbreviations

AE	Adverse Event
AP	Alkaline Phosphatase
AR	Adverse Reaction
BP	Blood Pressure
CK	Creatinine Kinase
CKD	Chronic Kidney Disease
CRC	Clinical Research Center
CRF	Case Report Form
CRP	C reactive protein
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EU	European Union
FF	Filtration Fraction
GCP	Good Clinical Practice
γ -GT	Gamma-Glutamyl-Transferase
HbA1c	Glycosylated Hemoglobin
HR	Heart Rate
hsCRP	high-sensitive CRP
ICH	International Conference on Harmonization
IRB	Institutional Review Board
LDL-C	Low Density Lipoprotein - Cholesterol
PI	Principal Investigator
PT	Premature Termination
RBC	Red Blood Cell Count
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard Deviation
SFU	Safety Follow-Up

SGOT	Serum Glutamate-Oxaloacetate-Transaminase
SGPT	Serum Glutamate-Pyruvate-Transaminase
SGLT	Sodium Glucose Transporter
SUSAR	Suspected Unexpected Serious Adverse Reaction
UV	Unscheduled Visit
WBC	White Blood Cell count
WHO	World Health Organization

1. Protocol summary

1.1. Design of the Trial

FINE study is a phase III, randomized (1:1), prospective, double-blind, placebo controlled, parallel-group, single centre study at the Clinical Research Center (CRC) of the Department of Nephrology and Hypertension, with its two separate locations:

- Erlangen, Ulmenweg 18, 91054 Erlangen and

- Nürnberg, Kreuzburger Str. 2, 90471 Nürnberg

After providing informed consent (visit 1), patients were tested for inclusion/exclusion criteria. Patients provided a blood sample for laboratory testing. If the patient then fulfilled inclusion criteria and in the absence of exclusion criteria, the patient was enrolled into the trial, the study visits were scheduled, and patient entered the 4 weeks run-in phase. At visit 2b, all baseline renal hemodynamic parameters including intraglomerular hemodynamic parameters were determined by the constant-infusion input clearance technique. Moreover, renal plasma flow following vitamin C and L-arginine infusion were determined. Each patient, after the baseline assessment of the renal parameters and assessment of renal plasma flow following the mentioned infusions was randomly assigned (1:1) to one of the two treatment arms (finerenone 10 mg or placebo) according to a randomization list. At the end of the visit all patients received respective advice to keep their medications stable during the study. A safety visit was conducted 2 weeks after first intake of study drug (visit 3). In case of no safety signals (in particular normal potassium level), finerenone 10mg was uptitrated to finerenone 20mg. Further safety visits took place 4 weeks and 8 weeks after randomization (visit 4 & visit 5). After 12 weeks of treatment (visits 6a and 6b), all parameters were reassessed.

<u>PT (premature termination) visit</u>

In case of withdrawal from the study, subject was asked to report to the clinical center for a PT visit. At the PT visit a physical examination was performed, vital signs were assessed, blood and urine samples were taken to perform a safety laboratory, a 12-lead ECG was performed, concomitant medications were checked, and AE was assessed. The date of withdrawal including the date of last treatment and the main reason for withdrawal was documented.

<u>SFU (Safety Follow-up) visit</u>

Only in case of ongoing AE and/or at the investigator’s discretion a SFU visit was performed. Relevant safety assessments: safety laboratory, urinalysis, vital signs, physical examination, 12-lead ECG, AE assessment, checking concomitant medication.

UV (Unscheduled Visit)

In case subjects was seen at additional times other than regular scheduled study visits, if deemed necessary by the Investigator, the following safety assessments were performed.

Relevant safety assessments: safety laboratory, urinalysis, vital signs, physical examination, 12-lead ECG, AE assessment, checking concomitant medication.

1.2. Trial Flow Sheet

Days	-28	-1	0	+14	+28	+56	+83	+84
Visit no.	1	2a	2b*	3*	4*	5*	6a	6b*
Demographic Data	X							
Vital signs	X		X	X	X	X		X
Physical examination	X		X	X	X	X		X
ECG	X		X	X	X	X		X
Informed Consent	X							
Inclusion / Exclusion Criteria	X							
Medical History	X							
Safety Laboratory	X		X	X	X	X		X
Urine Pregnancy Test □	X		X	X	X	X		X
Adverse Events	X	X	X	X	X	X	X	X
Check for concomitant medication	X		X	X	X	X		X
Examinations:								
Renal Constant-infusion input-clearance (PAH, Iohexol)			X					X
Assessment of renal oxidative stress (Vitamin C)			X					X
Assessment of stimulation of nitric oxide bioavailability (L-arginine)			X					X
24-urine sample		X	X				X	X
Cardio metabolic biomarkers (urine, serum)			X					X
Compliance Check + Med. Retrieval				X	X	X		X
Medication Dispense			X	X	X	X		
Up-titration of finerenone/placebo				X				

* a visit window of ± 3 days applies to visits 2b, 3, 4, 5, 6b; note that the actual "Study Day" may be different from the day shown due to the use of visit windows.

× blood samples are obtained in fasting except at visit 3, 4, 5

□ pregnancy testing in females of childbearing potential

2. Outcome Measures and Target Parameters

FINE study is an exploratory study. This means that all results, whether significant or not, will be interpreted. Consequently, the comparison of data between the verum and placebo groups can also be interpreted, since we are conducting not a confirmatory but a mechanistic, exploratory, hypothesis-generating study. In the study protocol, a primary objective was defined for the purpose of sample size calculation. However, this primary objective was not formulated in the same way as in large confirmatory studies. Keeping this in mind, the following key objectives are defined for further analysis:

A) To analyse the impact of finerenone on basal renal hemodynamics (renal plasma flow, glomerular filtration rate, filtration fraction, total renal vascular resistance) compared to placebo

B) To analyse the impact of finerenone on vasodilatory capacity to provocative maneuvers using L-arginine infusion and vitamin C infusion compared to placebo

C) To analyse the impact of finerenone on intraglomerular hemodynamics (resistance of the afferent and efferent arterioles and intraglomerular pressure) compared to placebo

D) To analyse the impact of finerenone on pulse wave (pulse wave velocity, pulse wave analysis) compared to placebo

E) To analyse the impact of finerenone on 24-h ambulatory blood pressure and vascular parameters compared to placebo

2.1. Safety

Safety assessments consisted of monitoring and recording all AE and serious AE (SAE), the regular monitoring of hematology, blood chemistry including potassium level and urine values, regular measurement of vital signs and the performance of physical examinations. AEs were collected from the time a subject signs the informed consent form until the visit 6b.

2.2. Analyses

Statistical analyses will be based on the basis of international guidelines (CPMP/ICH/363/96:E9).

2.3. Computer system and Software

The statistical analysis will be performed using Statistical Analysis System SPSS Version 31.0.0.0 (IBM SPSS Statistics, Chicago, Illinois, USA).

2.4. Protocol deviations and their Classification in Minor and Major

Prior to locking the trial data base, possible protocol deviations will be listed by the Study Data Manager. The classification in minor or major deviations will be done at the “Blinded Data Review Meeting”. The classification into minor or major deviations will be done in cooperation between the Prinicpal Investigator, the Co-Principal Investigator, the Data Manager and the responsible monitoring person. Major protocol violations will be protocol deviations, which are considered to interfere with the assessments of efficacy in this trial.

2.5. Analysis populations

For the analyses of the study, following populations are pre-specified:

The **Screened population (SCR population)** included all patients who provided informed consent and any demographic or baseline assessment.

The **Safety population (SAF population)** included all patients who had given at least one dose of study medication. It thus also includes patients without any efficacy measurements after randomisation.

The **Intention-to-treat population (ITT population)** consisted in all randomised patients having a post-baseline measurement of at least one efficacy parameter.

The **Per Protocol population (PP population)** included all patients of the ITT population who did not show any major protocol violation. These patients completed both clearance measurements during the study (visit 2b & visit 6b)

Use of analysis sets

Demographic data and clinical characteristics of the patients will be displayed on the SAF, the ITT, the PP populations. Prior and concomitant medications as well as prior and concomitant medical conditions will be reported on the SAF population.

The efficacy data will be displayed on the PP population. The PP population be the basis for the primary analysis, since this is a mechanistic study and not an endpoint trial. A secondary analysis will be done with the ITT (sensitivity analysis).

2.6. Definition of Derived Variables and Transformation of Variables

Derivations like change from baseline and/or previous visit are not mentioned in this chapter, but in the corresponding analysis section. Parameters used as objectives of the trial, will not be recalculated by programming as they are already calculated by the devices. Source data, resp. printouts delivered by the devices will be fixed up into the case report form (CRF).

2.6.1. Missing Values

Missing values in the CRF documented as “ND”, “NA” or “UNK” will usually not be entered into the database and the field will be blank.

If date parts are missing (the ‘day’ and/or the ‘month’) and there are calculations needed, a missing day will be replaced by ‘01’, a missing month will be replaced by ‘01’. A missing year will not be replaced. This does not apply for the date of study visits.

In case of the start date of an AE is missing, the date of first treatment intake (if appropriate) will be used as worst-case imputation, otherwise the first day/month instead of the middle will be taken also as a worst-case imputation.

Data of patients having withdrawn their consent to study participation at any time point during the study were not accounted for in the respective analyses up to the time point of withdrawal.

2.6.2. Subject Baseline Characteristics

In a general way, baseline values related to the patient’s condition and characteristics will be collected at Visit 1.

The baseline of efficacy parameters is visit 2b, the start of the randomised, double-blind phase. Baseline efficacy measurements will not be described explicitly as baseline characteristics, but shall be used in the efficacy tables and listings.

Body Mass Index (BMI) will be calculated as follows:

$$\text{BMI (kg/m}^2\text{)} = \text{weight} / \text{height}^2$$

2.6.3. Treatment Exposure and Compliance

Compliance by treatment and by visit

Records of study medication were kept during the study. Drug accountability was noted by the investigators.

2.7. Safety and Tolerability Measures

Safety assessments consisted of monitoring and recording all AE and serious AE (SAE), the regular monitoring of hematology, blood chemistry including potassium level and urine values, regular measurement of vital signs and the performance of physical examinations. AEs were collected from the time a subject sign the informed consent form until the visit 6b.

2.7.1. Adverse events

Information about all Adverse Events (AE), whether volunteered by the subject, discovered by investigator questioning or detected through physical examination, laboratory test or other means, were collected and recorded on the Adverse Event Case Report Form and followed as appropriate. An AE is any untoward medical occurrence, including an exacerbation of a pre-existing condition in a patient or clinical-trial subject administered a medicinal product which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g. abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. In clinical studies, an AE can include an undesirable medical occurrence at any time, even if no study treatment has been administered.

Medical conditions/diseases present before the study initiation were only considered AE if they worsen after the study initiation. Abnormal laboratory values or test results constitute AE only if they induce clinical signs or symptoms or require therapy, when they are recorded on the Adverse Events Case Report Form under the signs, symptoms or diagnosis associated with them.

Each adverse event was reported on an Adverse Event Case Report Form. As far as possible, each adverse event must also be described by:

1. its duration (start and end dates),
2. its severity grade (mild, moderate, severe, life-threatening, fatal)
3. its relationship to the study drug (suspected / not suspected)
4. treatment required and action taken with trial drug
5. outcome
6. seriousness
7. leading to discontinuation of the clinical trial (Yes/no)

As a minimum the following should be reported:

1. Study name

2. Patient identification (e.g. subject number, initials, sex, age)

3. Event (Preferably diagnosis)

4. Trial drug

5. Reporter

6. Causality

7. Outcome

Examples of the severity grade, relationship to study treatment and actions taken, as presented in the case report form, are provided below.

The severity grade of an adverse event provides a qualitative assessment of the extent or intensity of an adverse event, as determined by the investigator or as reported by the subject. The severity grade does not reflect the clinical seriousness of the event, only the degree or extent of the affliction or occurrence (e.g. severe nausea, mild seizure), and does not reflect the relationship to study drug.

Severity grade for an AE

1 = Mild

Signs and/or symptoms of which the patient is aware, but not interfering with patient's usual daily activity

2 = Moderate

Marked symptoms - discomfort enough to cause interference with usual activity

3 = Severe

Incapacitating with inability to work or do usual activity

4 = Life-threatening

Life-threatening consequences; urgent intervention indicated.

5 = death

Death related to AE

Causal relationship of AE

Medical judgment was used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship were recorded for each adverse event.

The investigator assessed the causality according to following definitions:

• Probable - Good reason and sufficient documentation to assume a causal relationship.

• Possible - A causal relationship is conceivable and cannot be dismissed.

• Unlikely - The event is most likely related to aetiology other than the trial product.

2.7.2. Serious adverse event

A SAE is an AE that fulfils 1 or more of the following criteria:

- Results in death

- Is immediately life-threatening

- Requires in-patient hospitalisation or prolongation of existing hospitalisation, unless hospitalization is for

o Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study hand has not worsened since signing the informed consent

- Results in persistent or significant disability or incapacity

- Is a congenital abnormality or birth defect

- Suspicion of transmission of infectious agents or

- based upon appropriate medical judgment, is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

2.7.3. Suspected unexpected serious adverse reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the applicable summary of product characteristics (Investigational brochure). The applicable Reference Document for this trial is the SmPC for finerenone (Kerendia®) in its current version.

2.7.4. Laboratory evaluations

During the study, blood and urine samples were drawn at pre-specified visits (details see above) to determine the following parameters:

Safety Laboratory Markers:

- Biochemistry panel incl. sodium, potassium, calcium, phosphate, urea, creatinine, eGFR (CKD-EPI formula), uric acid, Gamma-Glutamyl-Transferase (γ-GT), SGOT, SGPT,

Alkaline Phosphatase (AP), CK), fasting blood glucose, glycosylated haemoglobin (HbA1c), CRP, hsCRP

- Hematology incl. hemoglobin, hematocrit, red blood cell count (RBC), platelet count, white blood cell count (WBC).
- Urinalysis (by dipstick): incl. protein, glucose, blood, white blood cells, pH, ketonuria, nitrite

2.7.5. Vital signs

- Office BP measurements according to the recommendations of the WHO (mean from 3 measurements in a sitting position after 5 min rest and after one minute standing with an appropriate cuff size with an oscillometric device fulfilling quality assurance criteria).
- Measurement of HR in parallel with BP measurement.

2.7.6. Physical examination

Physical examination was performed at pre-specified visits and – when indicated – during the study course. Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/ Current Medical Conditions Case Report Form. Significant findings made after the start of study drug, which meet the definition of an AE, must be recorded on the Adverse Event Case Report Form.

3. Analysis

3.1. General Methodology

Descriptive statistics will be displayed for all documented and derived variables. For continuous variables, number of observations, mean, standard deviation, minimum, and maximum will be calculated. For categorical variables, number of patients, absolute and relative frequencies will be calculated.

In this parallel, placebo-controlled study, data analysis will be performed using unadjusted analysis, i.e. simple paired an unpaired t-test under the assumption of a normal distribution for the difference of interest.

In the first step of statistical analysis, the key objective parameters (see above) will be compared between baseline (visit 2b) and 12 weeks (visit 6b) within each group (paired analysis). In the second step, changes of the objective parameter after 12 weeks (visit 6b) of treatment will be compared between the finerenone group and the placebo group (unpaired

analysis). Third, the objectives measured at the end of the 12-week treatment phase will be directly compared between the finerenone and placebo group (unpaired analysis).

Normal distribution of the parameters is assessed by the Kolmogorov–Smirnov test before further analysis. Non-normally distributed parameters are analysed by Wilcoxon test and Mann–Whitney U test, respectively. Correlations are assessed using Spearmann and Pearson correlation coefficient for non-normally and normally distributed variables, respectively. A two-sided p value < 0.05 was considered statistically significant.

3.2. General Information about the Conduct of the Study

General information about the conduct of the trial will be displayed as follows:

- The date of first subject in, last subject out and trial duration (duration in days between the first subject in and the last subject out) will be described.

- The patient disposition (accounting of patients) will be presented by displaying the number of patients belonging to the different analysis populations.

- The number of discontinued subjects and the reasons for discontinuation, on the SCR population will be described.

3.3. Analysis of Demographic and other Baseline Characteristics

Demographic and patient characteristics will be summarized in tables and listings for the PP population, separated by treatment group and for the total population.

The demographic characteristics are: age and gender

Clinical characteristics at visit 1 will be described (in a table) for the PP population.

Summary of medical history and prior or concomitant medication will be presented.

The summary of medical history and current medical conditions including all previous and current medical conditions will be presented by preferred term and by body system of the system.

Baseline values of the efficacy measures will be presented in the efficacy section.

Baseline laboratory values will be presented.

Data from patients who were enrolled into the study, but not treated with study medication, will be presented in listings. No further analyses will be done with these patients' data.

3.4. Analysis of Efficacy

The primary analysis will be conducted on the PP population. Moreover, it will be repeated on ITT population.

The primary endpoint of this mechanistic study is to analyse:

- change of renal plasma flow following infusion of vitamin C infusion after finerenone treatment compared to placebo

The secondary endpoints of the study are to analyze:

- change of renal plasma flow following infusion of L-arginine after finerenone treatment compared to placebo
- change of renal plasma flow (para-aminohippurate clearance) after finerenone treatment compared to placebo
- change of glomerular filtration rate (iohexol clearance) after finerenone treatment compared to placebo
- change of filtration fraction after finerenone treatment compared to placebo
- change of renal vascular resistance after finerenone treatment compared to placebo
- change of resistance of the afferent arterioles (intraglomerular resistance) after finerenone treatment compared to placebo
- change of resistance of the efferent arterioles (intraglomerular resistance) after finerenone treatment compared to placebo
- change of intraglomerular pressure after finerenone treatment compared to placebo
- change of renal plasma flow following L-arginine infusion after finerenone treatment compared to placebo
- change of mean systolic 24-hour ambulatory blood pressure after finerenone treatment compared to placebo
- change of mean diastolic 24-hour ambulatory blood pressure after finerenone treatment compared to placebo
- change of mean day time systolic ambulatory blood pressure after finerenone treatment compared to placebo
- change of mean night time systolic ambulatory blood pressure after finerenone treatment compared to placebo
- change of mean day time diastolic ambulatory blood pressure after finerenone treatment compared to placebo
- change of mean night time diastolic ambulatory blood pressure after finerenone treatment compared to placebo
- change of mean systolic and diastolic dipping (24-hour ambulatory blood pressure) after finerenone treatment compared to placebo

- change of mean 24-hour, daytime and nighttime peripheral pulse pressure after finerenone treatment compared to placebo
- change of mean 24-hour, daytime and nighttime central pulse pressure after finerenone treatment compared to placebo
- change of mean 24-hour, daytime and nighttime central systolic blood pressure after finerenone treatment compared to placebo
- change of mean 24-hour, daytime and nighttime augmentation index at 75 beats per minute after finerenone treatment compared to placebo
- change of mean 24-hour, daytime and nighttime peripheral resistance after finerenone treatment compared to placebo
- change of mean 24-hour, daytime and nighttime pulse wave velocity after finerenone treatment compared to placebo
- change of mean 24-hour, daytime and nighttime heart rate after finerenone treatment compared to placebo
- change of central pulse pressure (office conditions) after finerenone treatment compared to placebo
- change of pulse wave velocity (office conditions) after finerenone treatment compared to placebo
- change of central systolic pressure (office conditions) after finerenone treatment compared to placebo
- change of pulse wave velocity (office conditions) after finerenone treatment compared to placebo
- change of augmentation index at 75 beats per minute (office conditions) after finerenone treatment compared to placebo
- change in mean serum potassium after finerenone treatment compared to placebo and the frequency of $K^+ > 5.5$ mmol/L in both treatment groups
- change in estimated glomerular filtration rate (eGFR) after finerenone treatment compared to placebo between visit 2b and visit 3
- change in estimated glomerular filtration rate (eGFR) after finerenone treatment compared to placebo between visit 2b and visit 6b

Further exploratory analysis:

- correlation of systemic inflammation (hsCRP) with pulse wave velocity at baseline and after treatment (finerenone, placebo)
- correlation of changes in systemic inflammation (hsCRP) with pulse wave velocity (finerenone andplacebo groups)
- correlation between changes in eGFR and serum potassium levels after treatment (finerenone, placebo)

The primary endpoint of this mechanistic study is the change renal plasma flow following vitamin C infusion after finerenone treatment compared to placebo.

Hence, (e.g.) the following null hypotheses H0, will be tested against their alternative hypotheses H1 using paired t-test:

H0: The change in renal plasma flow following infusion of vitamin C from baseline to post-treatment is the same with finerenone as with placebo.

H1: The change in renal plasma flow following infusion of vitamin C from baseline to post-treatment differs between finerenone and placebo.

3.5. Analysis of Safety and Tolerability

All safety analyses will be performed on the SAF population.

3.6. Adverse Events

Frequency tables for the preferred terms will be compiled, based on patients experiencing an AE and based on the number of AEs. They will be displayed with regard to severity and relationship to study drug. All AEs will be listed.

3.7. Criteria for clinically notable laboratory abnormalities

Please note: Normal ranges are given by the central laboratory of the University Hospital Erlangen-Nuremberg

Liver parameters: serum SGOT, SGPT, □-GT, AP > 300% of upper normal range

Renal parameters: decrease of eGFR (CKD-Epi) > 30%, serum potassium above the reference range at our central lab, serum sodium under the reference range at our central lab

Hematological parameters: Abnormal blood cell counts at baseline and changes of ≥ 20 % of blood cell counts.

Descriptive statistics of all laboratory values will be given.

Clinically notable laboratory abnormalities will be categorized by the principal investigator as relevant or not relevant. Relevant laboratory abnormalities will be excluded from the per protocol analysis.

3.8. Vital signs

Vital signs (for example mean systolic blood pressure, mean diastolic blood pressure, mean heart rate) will be analysed descriptively by appropriate methods, i.e. by presenting frequency distributions and/or basic summary statistics.

3.9. Multi-centre trial

This study was performed as a mono-centre study.

3.10. Subgroup analysis

Subgroup analysis is performed in the both the finerenone and placebo groups, all in an exploratory way.

Following subgroups are defined as of major interest:

- Age (according to the median of age)
- Baseline eGFR (according to the median of baseline eGFR)
- baseline systolic office BP at baseline (according to the median of systolic office BP)

3.11. Interim analysis

No interim analyses were planned.