A PHASE IV, REGISTRY-BASED, RANDOMISED, CONTROLLED, OPEN-LABEL TRIAL INVESTIGATING THE POTENTIAL FOR PATIROMER-FACILITATED USE OF HIGHER DOSES OF MINERALOCORTICOID ANTAGONISTS IN ADDITION TO STANDARD CARE (COMPARED TO STANDARD CARE ALONE) TO IMPROVE CONGESTION, WELL-BEING, MORBIDITY AND MORTALITY.

(RELIEHF)

FINAL ANALYSIS – STATISTICAL ANALYSIS PLAN

Study Title:	A Phase IV, registry-based, randomised, controlled, open-label trial investigating the potential for patiromer-facilitated use of higher doses of mineralocorticoid antagonists in addition to standard care (compared to standard care alone) to improve congestion, well-being, morbidity and mortality.
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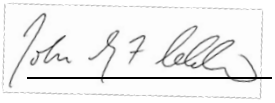
Approved by:	Professor John Cleland Professor of Cardiovascular and Metabolic Health School of Cardiovascular and Metabolic Health University of Glasgow		24th April '23
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1. INTRODUCTION

1.1. STUDY BACKGROUND

Poor control of congestion is a key unmet need for patients with heart failure. Congestion is an important cause of symptoms, disability and recurrent hospitalisation that commonly results in death due to heart failure, respiratory infection or multiple organ failure.

We plan to conduct a randomised controlled trial to investigate the potential of patiromer to facilitate the use of higher doses of MRA for patients with heart failure, worsening congestion and hyperkalaemia to find out whether this strategy improves the control of congestion and patient well-being and reduces morbidity and mortality.

1.2. STUDY OBJECTIVES

To investigate whether patiromer allows patients with worsening heart failure to be titrated to higher doses of MRA (predominantly spironolactone). Participants who are not assigned to patiromer should have titration to guideline-recommended doses of MRA attempted, although many are anticipated not to achieve this. Patients assigned to patiromer may be titrated to 200mg/day of spironolactone (highest licensed dose 400mg/day) or the highest licensed dose of eplerenone (50mg/day). (Eplerenone 50mg/day has similar MRA potency to about 35mg/day of spironolactone; accordingly, spironolactone is the preferred MRA. We expect that the median dose of spironolactone (or eplerenone) in the control group will be 25mg/day and that up to 25% will not tolerate any dose of MRA due to hyperkalaemia or other reasons.) We expect that the median dose of spironolactone in the patiromer-facilitated arm will be about 100mg/day because hypotension and renal dysfunction will prevent many patients from being titrated to 200mg/day and that almost all randomised patients will tolerate some dose of MRA.

1.3. STUDY DESIGN

A registry-based, randomised (two equal-sized groups), open-label trial.

1.4. RANDOMISATION

Eligible and consenting patients will be randomised on a 1:1 basis to the two groups using a mixed randomisation/minimisation algorithm that includes trial site, eGFR group (above or below 45ml/minute/1.73m^2) and systolic BP (above or below 110mmHg).

1.5. SAMPLE SIZE AND POWER

The anticipated primary endpoint rate in the control group is 40%. We estimate that 999 subjects per group (yielding 719 first-events) will provide >90% power to detect a hazard ratio of 0.75 (25% reduction) at the 1% significance level and >80% power to detect a hazard ratio of 0.80 at the 5% significance level, which we believe reflect clinically meaningful benefit. This is based on a time to first event analysis using the Wald statistic in a Cox proportional hazards model. To allow for some uncertainty the trial will be stopped

once 750 patients have experienced a primary endpoint. As the primary endpoint is a recurrent-event analysis, the trial should have additional power.

The primary endpoint at 60 days is a novel scoring system and therefore there are no prior data upon which to base assumptions. Assuming a normal distribution of "Congestion Index" scores, 400 patients provides >90% power to demonstrate a difference between strategies of 0.325 of a standard deviation in the effect size for the change in score between baseline and follow-up.

1.6. STATISTICAL ANALYSIS PLAN (SAP)

1.6.1. SAP OBJECTIVES

The objective of this SAP is to describe the reporting of the RELIEHF trial which was closed early with only 4 participants randomised.

1.6.2. GENERAL PRINCIPLES

Summaries for continuous variables, unless stated otherwise, will consist of number of values, number missing, mean, standard deviation, median, lower and upper quartiles, minimum and maximum. Summaries for categorical variables will consist of number of values, number missing and percentages.

1.6.3. DEVIATIONS TO THOSE SPECIFIED IN THE PROTOCOL

Due to the early closure of the trial, with only four participants randomised, no formal statistical analyses will be possible, therefore only summary statistics and/or listings will be produced.

1.6.4. ADDITIONAL ANALYSES TO THOSE SPECIFIED IN THE PROTOCOL

None.

1.6.5. SOFTWARE

Summaries will be produced using SAS for Windows v 9.4.

2. ANALYSIS

2.1. STUDY POPULATIONS

The screened population will consist of all patients screened, who met the inclusion criteria. The registry population will consist of all patients who consented to participate in the registry. The run-in population will consist of patients who consented to enter the randomised trial, who usually required a run-in phase to allow serum potassium to increase to >5.0 mmol/L. The randomised population consists of participants who were randomised.

2.2. STUDY STATUS

The disposition of patients from the screened population to the randomised population will be summarized. Reasons for not progressing to each phase will also be reported.

2.3. PROTOCOL DEVIATIONS

The protocol deviations will be categorised (major, minor etc.) and a listing produced for the randomised population.

2.4. SCREENING AND REGISTRY DATA

The following information will be summarised (if recorded) for each population separately (screened/registry).

Demographics

- Age (for screening only year of birth is recorded)
- Gender
- Ethnic group (white, mixed/multiple ethnic groups, asian/asian british, black/african/caribbean/black british, other ethnic group)
- Smoking status (current, former, never)
- Alcohol intake (none, occasional, frequent, heavy)
- In patient (yes, no)
- If in patient, heart failure cause of admission (yes, no) or heart failure a major contributor (yes, no)
- Duration of heart failure (<1 month, 1 to 6 months, >6 months to 12 months, >12 months to 18 months, >18 months)

Vital signs

- Weight
- Heart rhythm (sinus, atrial fibrillation, paced, other, unknown)
- Heart rate (screening only)
- SBP (screening only)
- DBP (screening only)
- Height

Aetiology of heart failure

- Ischaemic heart disease (yes, no)
- Idiopathic dilated cardiomyopathy (yes, no)
- Hypertension (yes, no)
- Mitral valve disease (yes, no)
- Aortic valve disease (yes, no)
- Hypertrophic cardiomyopathy (yes, no)
- Amyloid heart disease (yes, no)
- Atrial fibrillation (yes, no)

- Other (yes, no)
- Uncertain cause (yes, no)
- Primary cause (any of the above)

Medical history and co-morbidity (registry only)

- Coronary artery disease (yes, no)
- Diabetes (yes, no)
- Atrial fibrillation (yes, no)
- Stroke (yes, no)
- Severe cognitive dysfunction (yes, no)
- Chronic lung disease (yes, no)
- Cancer (yes, no)
- Other (yes, no)

Causes of worsening HF (registry only)

- Worsening cardiac function (yes, no)
- Worsening renal function (yes, no)
- Poor dietary compliance (yes, no)
- Poor medicines compliance (yes, no)
- Anaemia (yes, no)
- Infection (yes, no)
- Recent myocardial ischaemia or infarction (yes, no)
- New-onset atrial fibrillation (yes, no)
- Other arrhythmia (yes, no)
- Hypertension (yes, no)
- Iatrogenic (yes, no)
- Other (yes, no)
- Primary cause of worsening heart failure (any of the above)

Assessments/questionnaires (registry only – apart from Clinical frailty scale which is registry and screening)

- NYHA Class (I, II, III, IV)
- Symptom severity questionnaire
- Clinical frailty scale
- EQ5D VAS
- KCCQ

CV drugs (some types and doses only collected at registry)

- Furosemide oral (yes, no and (if yes) total daily dose category)
- Furosemide IV (yes, no and (if yes) total daily dose category)
- Bumetanide oral (yes, no and (if yes) total daily dose category)
- Bumetanide IV (yes, no and (if yes) total daily dose category)
- Torasemide oral (yes, no and (if yes) total daily dose category)
- Any ACE inhibitor (yes, no
- Specific ACE inhibitor – e.g. Ramipril (yes, no and (if yes) total daily dose category)

- Any ARB (yes, no
- Specific ARB – e.g. Candesartan (yes, no and (if yes) total daily dose)
- Sacubitril/valsartan (yes, no and (if yes) total daily dose)
- Any Beta-blocker (yes, no)
- Specific Beta-blocker – e.g. Carvedilol (yes, no and (if yes) total daily dose)
- Digoxin (yes, no and (if yes) total daily dose)
- Ivabradine (yes, no and (if yes) total daily dose)
- Any Thiazide (yes, no)
- Specific Thiazide – e.g. Metolazone (yes, no and (if yes) total daily dose)
- Any Calcium channel blocker (yes, no)
- Specific Calcium channel blocker – e.g. Amlodipine (yes, no)
- Nitrates (yes, no)
- Hydralazine (yes, no)
- Any Potassium sparing diuretic other than MRA (yes, no)
- Specific Potassium sparing diuretic other than MRA – e.g. Amiloride (yes, no)
- Any Potassium binding agent (yes, no)
- Specific Potassium binding agent– e.g. Patiromer (yes, no)
- Any Lipid lowering agent (yes, no)
- Specific Lipid lowering agent– e.g. Statin (yes, no)
- Any Antiplatelet (yes, no)
- Specific Antiplatelet – e.g. Aspirin (yes, no)
- Any Anticoagulant (yes, no)
- Specific Anticoagulant – e.g. Warfarin (yes, no)
- Any MRA (yes, no and (if yes) total daily dose)
- Specific MRA – e.g. Spironolactone (yes, no and (if yes) total daily dose)
- If no MRA at screening, was one taken in last month (yes, no)

Non-CV drugs (screening only collects NSAID other than aspirin and hypoglycaemic therapy)

- NSAIDs other than aspirin (yes, no)
- Any Hypoglycaemic therapy (yes, no)
- Specific Hypoglycaemic therapy – e.g. Insulin (yes, no)
- Any SGLT2 (yes, no and (if yes) total daily dose)
- Specific SGLT2 – e.g. Canagliflozin (yes, no and (if yes) total daily dose)
- Antibiotics (yes, no)
- Any Oral steroids (yes, no and (if yes) total daily dose)
- Specific Oral steroids – e.g. Prednisolone (yes, no and (if yes) total daily dose)
- Any Inhaled medicines (yes, no)
- Specific Inhaled medicines – e.g. Beta2 agonist (yes, no)
- Oral iron (yes, no)
- Any IV iron therapy (yes, no)
- Specific IV iron – e.g. Ferric carboxymaltose (yes, no)
- Any Treatment for indigestion (yes, no)
- Specific Treatment for indigestion – e.g. Proton pump inhibitor (yes, no)

- Other non-cv drug therapy (yes, no)

Oedema (registry only)
- Lying down in previous hour (yes, no)
- Swelling of leg/ankles (none, mild, moderate, severe)
- Above right ankle circumference
- Above left ankle circumference

Orthopnoea test (registry only)
- Completed (yes, no, part completed – if no or part completed, reason)
- Heart rate before test
- Respiratory rate before test
- Diastolic blood pressure before test
- Systolic blood pressure before test
- Heart rate after test
- Respiratory rate after test
- Diastolic blood pressure after test
- Systolic blood pressure after test

Bloods (screening only)
- Serum sodium
- Serum potassium
- Urea
- Serum creatinine
- eGFR (CKD-EPI – calculated)

Haematology and Biochemistry Bloods (registry only)
- Hb
- MCHC
- WBC
- Neutrophils
- Lymphocytes
- Serum sodium
- Serum potassium
- Bicarbonate
- Calcium
- Phosphate
- Urea
- Serum creatinine
- eGFR (CKD-EPI – calculated)
- Bilirubin
- ALT

- AST
- ALP
- Albumin
- Magnesium
- BNP
- NT-proBNP
- Serum iron
- Transferrin saturation
- Ferritin

Spot urine test (registry only)

- Albumin/creatinine ratio

Echocardiogram

- LVEF
- Systolic dysfunction (none, mild, moderate, severe)
- HF subgroup (HFrEF, HFmrEF, HFpEF)
- Left atrial enlargement (none, mild, moderate, severe)
- Valve disease: mitral regurgitation (none, mild, moderate, severe)
- Valve disease: aortic stenosis (none, mild, moderate, severe)
- Valve disease: tricuspid regurgitation (none, mild, moderate, severe)
- Valve disease: other (none, mild, moderate, severe)
- Pulmonary hypertension (none, mild, moderate, severe)
- LV end-diastolic dimension (registry only)
- Left atrial dimension (registry only)

Physical examination (registry only)

- Jugular venous pressure (not visible, normal, raised 4-10 cm, raised > 10 cm)
- 3rd heart sound (present, absent)
- Lung crepitations (absent, unilateral, bilateral basal, bilateral to mid-zone, all lung fields)
- Hepatomegaly (present, absent)

12-lead ECG (registry only)

- Heart rate
- Heart rhythm (sinus, AF, paced, other)
- Paced (yes, no)
- LBBB (yes, no)
- RBBB (yes, no)
- IVCD (yes, no)
- Within normal limits (yes, no)

10m walk test (registry only)

- Duration (1st attempt)

- Duration (2nd attempt)
- Duration (3rd attempt)
- Breathlessness rating after final test
- Fatigue rating after final test
- Respiratory rate after final test
- Heart rate after final test

COVID vaccine/history (registry only – for those enrolled after January 2020)

- COVID vaccine (yes, no)
- COVID infection (yes, no)

2.5. RUN-IN DATA

For those who entered the run-in phase, the following information (recorded at the start and end of run-in) will be reported (summary table and listing):

- Weight
- SBP
- Type of MRA given
- Total daily dose of MRA given
- Serum sodium
- Serum potassium
- Serum creatinine
- Urea

2.6. RANDOMISED DATA

The following information is collected for the randomised population. Due to the small number of randomised participants, the data will by listed (in excel files) but no summary tables will be produced:

Randomisation visit – vital signs; concomitant CV therapy; concomitant non-cv therapy; NYHA Class; symptom severity questionnaire; oedema grade; orthopnoea test; haematology; biochemistry; physical exam; EQ-5D VAS; KCCQ; 12-lead ECG; 10m walk test.

Days 3/5/14/30 and months 3/9/15 and end of study – MRA details; patiromer details; compliance (researcher and participant opinion); vital signs; concomitant CV therapy; NYHA Class; symptom severity questionnaire; patient global assessment; oedema grade; labs (as for screening visit).

Days 7/60 and months 6/12 – as above (apart from labs) plus concomitant non-cv therapy; orthopnoea test; haematology; biochemistry; physical exam; EQ-5D; KCCQ; 12-lead ECG; 10m walk test.

2.7. SAFETY DATA

SAEs and non-serious adverse reactions for the randomised population will be listed. SAEs for the registry population will also be listed.

3. TABLES

Dummy reports will be produced and reviewed by the chief investigator. Approval of the content of the final report will be documented prior to database lock.

4. LISTINGS

Listings of all derived datasets will be produced as excel spreadsheets.

5. DOCUMENT HISTORY

This is the first version of the SAP, initial creation.