Effect of Short-Term Prednisone Therapy on C-reactive protein Change in Emergency Department Patients With Acute Heart Failure and Elevated Inflammatory Markers (CORTAHF)

Protocol Number: CHF202301

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Funded by: Heart Initiative

Version Number: Final v. 2.0

5 January 2024

Protocol Signature Page

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Declaration of Investigator:

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Site Principal Investigator Name: _____

Site Principal Investigator Signature: _____

Date of Signature: _____

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
Throughout	Reference changed from study days 30 and 90 to study days 31 and 91.	To clarify that these assessments are to be performed 30 and 90 days after randomization, which are days 31 and 91 counting the day of randomization as day 1.
1.2	Timing between assessments corrected in study schema.	Previous intervals were incorrect, although corrected schema provided to investigators during pre-study training.
1 3 8.1.5 9.4.3 9.4.9	Secondary objective and endpoint revised to include all adverse events of worsening heart failure through day 91. The previous secondary endpoint, with a more restricted WHF definition, and more limited timeframe moved to tertiary/exploratory endpoint.	This is a small pilot study with a small number of events expected. A longer timeframe and less stringent definition of WHF should provide more power to detect an effect on this measure of mortality/morbidity.
3 9.4.9	Exploratory endpoints of length of stay in ICU and length of initial hospital stay limited to the 30 days following randomization	The vast majority of patients will be discharged before study day 31. However, in order to account for a few possible extreme values, these endpoints will be truncated at 30 days.
3 9.4.9	Dyspnea removed from list of HF symptoms.	Dyspnea on exertion will be captured using NYHA class. No separate measure of dyspnea will be captured.
1.3 8.1.7	Local laboratory assessments at days 2 and 4 are to be recorded if done but are not required.	To reduce site burden and study cost, these assessments will be optional and will be collected per local practice. The omission will not affect the main study objectives.
9.3	The main analysis will be performed in the per-protocol rather than the intention-to-treat analysis population. The ITT population will exclude patients randomized in error.	Because this is a small pilot study, a few inappropriately enrolled or treated patients can have a major effect on the findings. Thus, the main analysis will be conducted in the per-protocol population which excludes patients enrolled who were ineligible or who were not treated according to the allocated treatment. Analyses will exclude patients who were randomized in error, e.g., non-existent patients or patients found to be ineligible before study treatment started.
10.3	Amendment history updated to include this amendment.	Rationales for changes provided above.

Contents

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and any applicable local regulatory requirements. Investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of this clinical trial have completed ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Ethics Committee (EC) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor, funding agency and documented approval from the EC, except where necessary to eliminate an immediate hazard(s) to the trial participants. In addition, all changes to the consent form will be EC approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Effect of Short-Term Prednisone Therapy on C-reactive protein Change in Emergency Department Patients With Acute Heart Failure and Elevated Inflammatory Markers (CORTAHF)

Study Description: This is a multicenter, parallel-group, randomized, open-label, controlled trial. Patients with a diagnosis of acute heart failure (AHF) in the emergency department (ED) or after emergency presentation to hospital will be screened and informed of the study. After signed consent, patients will be randomized into the control group (usual AHF treatment) or intervention group (usual AHF treatment + prednisone). Prednisone will be given for 7 days. Patients will be assessed at days 2, 4 or at discharge if earlier, and at day 7 at hospital visit. If the patient has been discharged before day 7, a follow-up visit will be scheduled at day 7 for endpoints assessment followed by a scheduled hospital visit at day 31 and a telephone follow-up at day 91. Study drug will be dispensed for the patient to take home until day 7.

Objectives: Primary objective: to assess the effects of prednisone therapy started in the ED/hospital and continued for up to 7 days on the change of CRP level.

Secondary objectives: to compare the effects of prednisone therapy on the occurrence of death, hospital readmission for HF, or worsening HF (WHF) through day 91; and on change in quality of life (QoL) as measured by the EQ-5D-5L questionnaire at day 7.

Other objectives include comparisons on the effects on WHF, death or HF readmission through day 31, change in QoL at day 31, symptoms and signs of heart failure at day 7 including weight, and all-cause mortality or hospital readmission for HF through day 91.

Endpoints: Primary endpoint: change of CRP level, defined by CRP level at day 7 minus CRP level at inclusion

Secondary Endpoints:

1. Time to first event of WHF adverse event, death, or hospital readmission for decompensated HF to day 91.
2. Changes in quality of life measured by the EQ-5D-5L from randomization to day 7.

Study Population: 120 adult patients visiting the ED or presenting emergently to the hospital with a diagnosis of AHF and elevated markers of congestion and inflammation.

Inclusion criteria:

1. Age 18 to 85 years of age
2. Unplanned ED visit or hospital presentation within the 12 hours prior to Screening with acute or worsening dyspnea and/or orthopnea, and pulmonary congestion on chest X-ray or lung ultrasound.
3. All measures from presentation to randomization of systolic blood pressure ≥ 100 mmHg, and of heart rate ≥ 60 bpm.

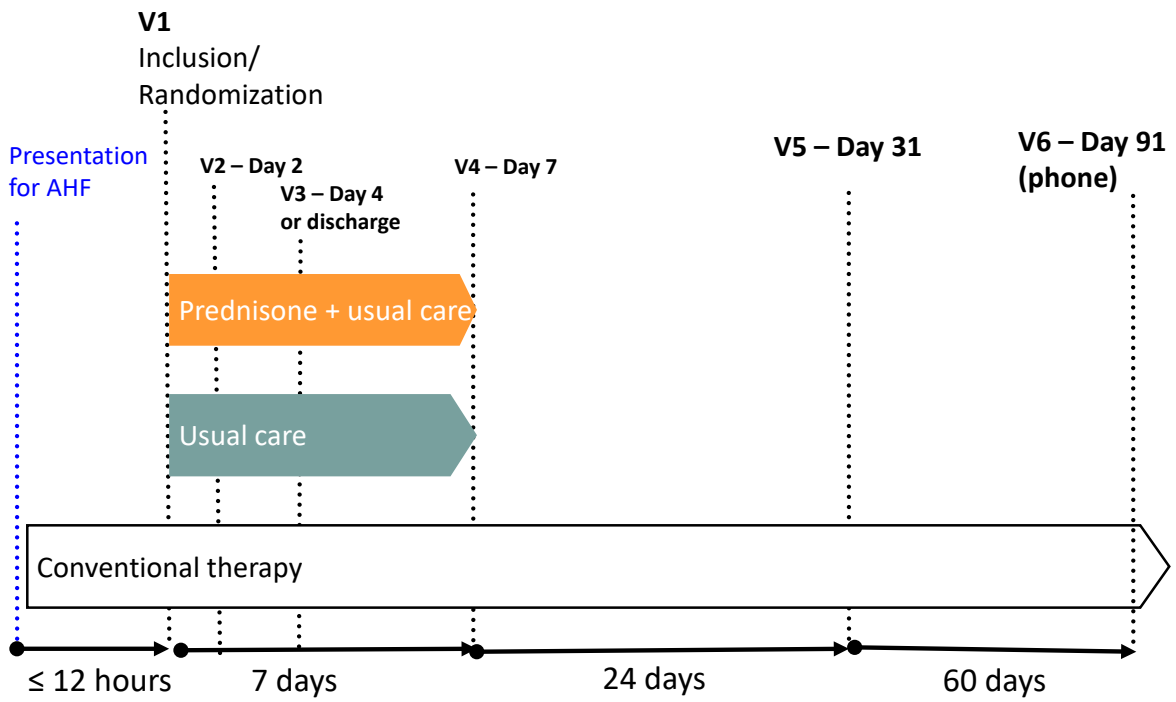
4. Written informed consent to participate in the study.
5. Biomarker levels indicative of congestion and inflammation: At Screening, NT-proBNP > 1,500 pg/mL and CRP > 20 mg/L
6. Patient agrees for follow-up visits at the hospital at day 7 in case of earlier discharge and Day 31.

Exclusion criteria:

1. Anticipated life expectancy less than 6 months
2. Mechanical ventilation (not including CPAP/BIPAP) prior to Screening.
3. Significant pulmonary disease contributing substantially to the patients' dyspnea such as FEV1< 1 liter or need for chronic systemic or non-systemic steroid therapy, or any kind of primary right heart failure such as primary pulmonary hypertension or recurrent pulmonary embolism.
4. Myocardial infarction, unstable angina or cardiac surgery within 3 months, or cardiac resynchronization therapy (CRT) device implantation within 3 months, or percutaneous transluminal coronary intervention (PTCI), within 1 month prior to inclusion.
5. Index Event (admission for AHF) triggered primarily by a correctable etiology such as significant arrhythmia (e.g., sustained ventricular tachycardia, or atrial fibrillation/flutter with sustained ventricular response >130 beats per minute, or bradycardia with sustained ventricular arrhythmia <45 beats per minute), infection, severe anemia, acute coronary syndrome, pulmonary embolism, exacerbation of COPD, planned admission for device implantation or severe non-adherence leading to very significant fluid accumulation prior to admission and brisk diuresis after admission. Troponin elevations without other evidence of an acute coronary syndrome are not an exclusion.
6. Uncorrected thyroid disease, active myocarditis, or known amyloid or hypertrophic obstructive cardiomyopathy.
7. History of heart transplant or on a transplant list, or using or planned to be implanted with a ventricular assist device.
8. Sustained ventricular arrhythmia with syncopal episodes within the 3 months prior to screening that is untreated.
9. Presence at screening of any hemodynamically significant valvular stenosis or regurgitation, except mitral or tricuspid regurgitation secondary to left ventricular dilatation, or the presence of any hemodynamically significant obstructive lesion of the left ventricular outflow tract.
10. Primary liver disease considered to be life threatening
11. Renal disease or eGFR < 30 or > 80 mL/min/1.73m^2 (as estimated by the simplified MDRD formula) at inclusion or history of dialysis.
12. Systemic steroid therapy, within 30 days from inclusion.
13. Inability to consent, or patient under guardianship measure
14. Participation in another intervention trial in the past 30 days
15. Anticipated non-adherence to study protocol or follow-up.
16. Pregnant or nursing (lactating) women.
17. Known hypersensitivity to steroids or constituents of prednisone tablets (excipients)

	18. Psychotic states not yet controlled by treatment 19. Concomitant administration of live vaccines and up to 3 months after end of corticotherapy administration. 20. Patient under legal protection measure (tutorship or curatorship) and patient deprived of freedom 21. Persons subject to psychiatric care without their consent
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	5 hospitals in Armenia
Description of Study Intervention:	Investigational product: Prednisone 40 mg once a day, for up to 7 days added to usual care medications. Comparator: Usual care alone.
Study Duration:	13 months (including recruitment (12 months), Follow up (1 month for the last patient enrolled)
Participant Duration:	91 days

1.2 SCHEMA


V1
Inclusion/
Randomization
Presentation
for AHF
V2 – Day 2
V3 – Day 4
or discharge
V4 – Day 7
V5 – Day 31
V6 – Day 91
(phone)
Prednisone + usual care
Usual care
Conventional therapy
≤ 12 hours
7 days
24 days
60 days

1.3 SCHEDULE OF ACTIVITIES (SOA)

Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 Telephone Contact
	Inclusion and randomization, ≤ 12h after ED/hospital presentation	Day 2 ~24 hours after randomization	Day 4 ~72 hours after randomization, or discharge if earlier	Day 7 7 (+/-1) days after randomization	Day 31 30 (+/- 5) days after randomization	Day 91 90 (+/- 5) days after randomization
Eligibility	X					
Pregnancy test for women of childbearing age	X					
Medical history	X					
Chest X-ray/ lung US*	X					
ECG*	X					
Echocardiography†	X					
Concomitant medications	X	X	X	X	X	
NT-proBNP, Tn, CRP	X	X (CRP only)	X (CRP only)	X (CRP only)	X	
Local labs: Hgb, serum sodium, glucose, potassium and kidney function measures, WBC count, % lymphocytes, liver function	X	X§	X§	X	X	
Physical exam including vital signs and clinical HF assessment	X	X	X	X	X	
EQ-5D-5L	X			X	X	
Biobanking samples	X		X	X	X	
Randomization	X					
Study drug prednisone‡ or usual care	X (seven days of treatment for investigational arm only)					
Clinical outcomes	←----------X---------->					X
Adverse events	<----------X---------->					

*Non-study assessment considered standard of care required for study eligibility.
†Non-study assessment considered standard of care which should have been performed within 6 months prior to inclusion, including during the current admission.
‡In patients randomly assigned to active intervention.
§To be recorded if done per local practice, but not required.

2 INTRODUCTION

2.1 STUDY RATIONALE

Acute heart failure (AHF) is a common discharge diagnosis in the emergency department (ED), associated with 1-month mortality of 6%, and a 30% risk rate of 1-month rehospitalization (Metra et al., 2019; Arrigo et al., 2020). AHF is also associated with a high risk of early worsening clinical state, with a reported rate of 10-14% at day 7 (Cannon et al., 2015; Cotter et al., 2008). Current guidelines recommend the use of nitrates and low dose diuretic to treat congestion, but to date, no drug has ever shown any improved clinical outcome when given at the acute phase (Mebazaa et al., 2015).

Several studies suggest that there is a high inflammatory component in AHF (Goonewardena et al, 2016), with elevated markers such as IL6 and C-reactive protein (CRP). As it is the case in other acute respiratory disease, a short course of steroid therapy may limit the inflammatory response and in turn, improve AHF prognosis.

The objective of the study is to assess the effect of a 7-day course of steroid introduced in the ED or early in the hospitalization on inflammatory response.

2.2 BACKGROUND

The lack of clinical benefit of current recommendations was confirmed in the recent ELISABETH RCT that included 503 patients aged > 75 years in 15 EDs in France. In this trial, the overall 1 month mortality of patients aged > 75 years after AHF was 10%, with a mean of 16 days alive and out of hospital at day 30 (Freund et al, 2020).

Several markers of inflammation such as CRP, IL6 or monocytes are reportedly higher in patients with AHF than in healthy subjects. Furthermore, studies report an association between inflammatory markers (IL6 and CRP) and worse prognosis (Kalogeropoulos et al, 2014; Davison et al, 2021). A doubling of IL6 level was associated with an increased risk of hospital admission (OR 1.31 [1.11 – 1.61]) and increased death at 180 days (OR 1.33 [1.15 – 1.54) and patients that had a persistent elevated CRP at 30 days are reportedly at higher risk of death (OR 2.29 [1.16 – 4.52]).

Preliminary studies have suggested that a short course (7 days) of low dose (40 mg) steroids therapy (burst) may help improve prognosis in patients with heart failure partially because a potent diuretic effect (Liu, Zhao et al, 2016; Liu, Ge et al, 2016; Liu et al 2007). Usual recommended dose is 40 mg of prednisone or its equivalent (6mg dexamethasone), for a 5 to 7 days period. An early short course of steroid (prednisone or dexamethasone) have been proved to improve short term prognosis in patients with acute respiratory disease such as chronic obstructive pulmonary disease exacerbation, asthma or COVID-19 (Le Conte et al, 2019; Wedzicha et al., 2017; The RECOVERY Collaborative Group, 2021). This early treatment is reportedly associated with side effects such as sepsis, thrombo-embolic event and fracture, with a global risk of less than 2 per 1000 patients-years (Yao et al, 2020). Concerns were also raised about the potential detrimental effects of a short course of low dose steroids, which could be associated to a higher risk of heart failure exacerbations with an incidence rate of 1.3 per 1000 patients-years. However, this risk was limited in time and was attenuated after 30 days (Yao et al, 2020).

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 Known Potential Risks

Steroid burst treatment (40mg during 7 days) has been reported to carry risk of fracture, thrombo-embolism event, gastro-intestinal bleeding and heart failure. However, these risks were reported as low with very low incidence (less than 2 per 1000 Persons years) [Yao et al, 2020; Burstin et al, 2002]. This treatment is reportedly associated with a global risk of less than 2 per 1000 patients-years,

with side effects that includes sepsis, thrombo-embolic event, and fracture. Steroids could also be associated to a higher risk of heart failure with an incidence rate of 1.3 per 1000 patients-years. However, this risk has been reported as limited in time and was attenuated after 30 days.

2.3.2 Known Potential Benefits

AHF carries an important mortality in the first month following ED visit (6% for all patients, and up to 10% in patients aged 75 years and over). The overall burden of AHF is high and also includes a high risk of return visit to the ED, rehospitalization and poorer quality of life.

If our hypothesis is confirmed, the CORTAHF study will be the first to suggest the efficacy of a simple and unexpensive treatment in patients with AHF that could reduce inflammation, which in turn could improve prognosis.

Furthermore, this pilot study would allow to have an estimation of the effect of this treatment and pave the way to the conduction of further phase 3 trials focused on clinical endpoints and larger validation studies, and the development and use of other anti-inflammatory agent in this indication.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To assess the effects of prednisone therapy started in the ED and continued for up to 7 days on the change of CRP level	Change in CRP level at 7 days	CRP levels increase rapidly in response to trauma, inflammation and infection and decrease rapidly with resolution of these conditions (Du Clos 2000). Thus, CRP measurement is widely used to monitor inflammatory states.
Secondary		
To compare the effects on the occurrence of death, hospital readmission for HF or worsening HF (WHF) through day 91	The composite of first event of a WHF adverse event, hospital readmission for HF, or death through day 91	WHF has been shown to be associated with longer hospital stay and increased risk of HF readmission and death, and HF readmission and death are outcomes representing disease progression. The composite is a generally accepted endpoint in AHF trials. For this pilot study, the definition of WHF has been expanded to include all reported adverse events of WHF (not only those requiring intensification of IV therapy or mechanical support) over a broader timeframe (longer than 7 days).
To compare the effects on change in quality of life (QoL) as measured by the EQ-5D-5L questionnaire at day 7	Changes in quality of life measured by the EQ-5D-5L from randomization to day 7	Quality of life, encompassing functional capacity, psychological status, and frequent rehospitalizations may be particularly important to patients (Nieminen, Dickstein et al. 2015) The EQ-5D is a validated, standardized instrument developed by EuroQol.
Tertiary/Exploratory		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To compare the effects on the occurrence of death, hospital readmission for HF or worsening HF (WHF) through day 31	The composite of WHF, death, or hospital readmission for decompensated HF at day 31. WHF is defined as worsening signs and/or symptoms of HF that require an intensification of intravenous therapy (including initiation or re-initiation or dose increase) for HF or mechanical ventilatory, renal or circulatory support (occurring between 24 hours after randomization and the earlier of discharge or day 7).	WHF has been shown to be associated with longer hospital stay and increased risk of HF readmission and death, and HF readmission and death are outcomes representing disease progression. The composite is a generally accepted endpoint in AHF trials.
To compare the effects on the occurrence of death, hospital readmission for HF or worsening HF (WHF) through day 91	The composite of WHF, death, or hospital readmission for decompensated HF at day 91. WHF is defined as worsening signs and/or symptoms of HF that require an intensification of intravenous therapy (including initiation or re-initiation or dose increase) for HF or mechanical ventilatory, renal or circulatory support (occurring between 24 hours after randomization and the earlier of discharge or day 7).	HF readmission and death are outcomes representing disease progression. The composite is a generally accepted endpoint in AHF trials.
To compare the effects on change in quality of life (QoL) as measured by the EQ-5D-5L questionnaire at day 31	Changes in quality of life measured by the EQ-5D-5L from randomization to day 31	To explore longer-term effect on quality of life.
To compare the effects on symptoms and signs of heart failure at day 7 including weight	Changes from randomization to day 7 in: • NYHA classification, • orthopnea, • peripheral edema, • rales, • jugular venous pulse, and • body weight.	NYHA class (dyspnea at rest or on exertion) is a measure of patient symptom severity. The other measures reflect congestion (fluid retention). Both symptom improvement and decongestion (which is related to symptoms) reflect important therapeutic goals.
To compare the effects on all-cause mortality or Hospital readmission for HF through day 91	• Death from any cause to days 31 and 91 • Readmission for HF or death to days 31 and 91 • HF re-admission through days 31 and 91.	HF readmission and death are outcomes representing disease progression. The composite is a generally accepted endpoint in AHF trials.
To support findings of primary analyses and to suggest further hypotheses for later research.	Requirement for treatment with intravenous vasopressors, inotropes, and/or mechanical ventilatory, renal or circulatory support or death from randomization through day 7 (“treatment failure”).	These treatments represent therapeutic failure.
	Changes from randomization to day 7, and to day 31, in biomarker levels including brain natriuretic peptide	Natriuretic peptide levels reflect congestion, creatinine reflects renal function, and troponin reflects myocardial damage.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	(BNP), NT-pro-BNP, creatinine and troponin.	Effective HF therapy may reduce congestion, increase renal function and reduce cardiac damage.
	Time to worsening heart failure through the earlier of day 7 or discharge.	WHF has been shown to be associated with longer hospital stay and increased risk of HF readmission and death.
	Length of stay in ICU through 30 days following randomization	Reducing time in intensive care is an important therapeutic goal.
	Length of initial hospitalization through 30 days following randomization	Reducing time in hospital is an important therapeutic goal.
	Days dead or in acute care (including all intensive acute care units) out of the first 30 days following randomization.	This endpoint is another way to assess reduction of time in intensive care.
	Days dead or in the hospital out of the first 30 days following randomization.	This endpoint is another way to assess reduction of time in hospital.
	Hospital readmission through days 31 and 91	All-cause readmission can provide further information re effects on admissions for only HF.

4 STUDY DESIGN

4.1 OVERALL DESIGN

CORTAHF is a parallel-group, comparative, open-label, randomised (1:1), controlled trial. Patients with a diagnosis of AHF in the ED or after emergency presentation to hospital will be screened and informed of the study. After signed consent, patients will be randomized into the control group (usual AHF treatment) or intervention group (usual AHF treatment + prednisone).

Prednisone will be given for 7 days. Patients will be assessed at days 2, 4 or at discharge if earlier, and at day 7 at hospital visit. If the patient has been discharged before day 7, a follow-up visit will be scheduled at day 7 for endpoints assessment followed by a scheduled hospital visit at day 31 and a telephone follow-up at day 91. Study drug will be dispensed for the patient to take home until day 7.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A double-blind design would be preferred to the open-label design, but prohibitively expensive given available resources. The primary outcome, as well as the clinical outcomes including rehospitalization and death, are objective measures which should not be subject to overt bias.

4.3 JUSTIFICATION FOR DOSE

Oral “burst” of steroids are used and recommended in acute respiratory disease such as COPD or asthma exacerbation, or COVID-19. Recommended dose for burst is 40 mg prednisone once a day during 7 days.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Age 18 to 85 years of age
2. Unplanned ED visit or hospital presentation within the 12 hours prior to Screening with acute or worsening dyspnea and/or orthopnea, and pulmonary congestion on chest X-ray or lung ultrasound.
3. All measures from presentation to randomization of systolic blood pressure ≥ 100 mmHg, and of heart rate ≥ 60 bpm.
4. Written informed consent to participate in the study.
5. Biomarker levels indicative of congestion and inflammation: At Screening, NT-proBNP > 1,500 pg/mL and CRP > 20 mg/L
6. The patient agrees for follow-up visits at the the hospital at day 7 in case of earlier discharge and Day 31.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Anticipated life expectancy less than 6 months
2. Mechanical ventilation (not including CPAP/BIPAP) prior to Screening.
3. Significant pulmonary disease contributing substantially to the patients' dyspnea such as FEV1< 1 liter or need for chronic systemic or non-systemic steroid therapy, or any kind of primary right heart failure such as primary pulmonary hypertension or recurrent pulmonary embolism.
4. Myocardial infarction, unstable angina or cardiac surgery within 3 months, or cardiac resynchronization therapy (CRT) device implantation within 3 months, or percutaneous transluminal coronary intervention (PTCI), within 1 month prior to inclusion.
5. Index Event (admission for AHF) triggered primarily by a correctable etiology such as significant arrhythmia (e.g., sustained ventricular tachycardia, or atrial fibrillation/flutter with sustained ventricular response >130 beats per minute, or bradycardia with sustained ventricular arrhythmia <45 beats per minute), infection, severe anemia, acute coronary syndrome, pulmonary embolism, exacerbation of COPD, planned admission for device implantation or severe non-adherence leading to very significant fluid accumulation prior to admission and brisk diuresis after admission. Troponin elevations without other evidence of an acute coronary syndrome are not an exclusion.
6. Uncorrected thyroid disease, active myocarditis, or known amyloid or hypertrophic obstructive cardiomyopathy.
7. History of heart transplant or on a transplant list, or using or planned to be implanted with a ventricular assist device.
8. Sustained ventricular arrhythmia with syncopal episodes within the 3 months prior to screening that is untreated.
9. Presence at screening of any hemodynamically significant valvular stenosis or regurgitation, except mitral or tricuspid regurgitation secondary to left ventricular dilatation, or the presence of any hemodynamically significant obstructive lesion of the left ventricular outflow tract.
10. Primary liver disease considered to be life threatening

11. Renal disease or eGFR < 30 or > 80 mL/min/1.73m^2 (as estimated by the simplified MDRD formula) at inclusion or history of dialysis.
12. Systemic steroid therapy, within 30 days from inclusion.
13. Inability to consent, or patient under guardianship measure
14. Participation in another intervention trial in the past 30 days
15. Anticipated non-adherence to study protocol or follow-up.
16. Pregnant or nursing (lactating) women.
17. Known hypersensitivity to steroids or constituents of prednisone tablets (excipients)
18. Psychotic states not yet controlled by treatment
19. Concomitant administration of live vaccines and up to 3 months after end of corticotherapy administration.
20. Patient under legal protection measure (tutorship or curatorship) and patient deprived of freedom
21. Persons subject to psychiatric care without their consent

5.3 LIFESTYLE CONSIDERATIONS

Note prohibited medications in Section 6.5.2.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial may be re-screened and included if all eligibility criteria are met upon re-evaluation.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients will be screened and included in the ED or after emergency presentation to the hospital after informed consent is signed.

	Number of participants
Total number of participants to be randomized	120
Number of centers	5
Enrolment period (months)	12
Number of participants/center	24
Number of participants/center/month	**2**

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 Study Intervention Description

Prednisone 40 mg will be administered in tablets. Prednisone is a corticosteroid (also called steroidal anti-inflammatory drug). This medicine belongs to the pharmacotherapeutic class of glucocorticoids, systemic use.

This medicine is reserved for adults and children over 6 years old and over 20 kg.

This drug is used in many diseases, where it is used for its anti-inflammatory effect. Its action is useful in the treatment of many inflammatory or allergic conditions.

6.1.2 Dosing and Administration

Dosage: 40 mg once a day to be taken during 7 days (taken with or without meals).

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 Acquisition and accountability

Hospital pharmacies will dispense the investigational drugs to the patient in accordance with the specific research prescription completed and duly signed by the investigator. Only one dispensation (for 7-day supply) will be needed per patient.

6.2.2 Formulation, Appearance, Packaging, and Labeling

Prednisone tablets available in the hospital pharmacy will be dispensed.

6.2.3 Product Storage and Stability

This medicinal product does not require any special storage precautions. The pharmacist is responsible for ensuring adequate storage conditions for drugs.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The randomization list will be generated by a central statistician. A centralized randomization will be implemented for the study. Patients meeting eligibility criteria will be randomized either to intervention group (usual care + prednisone) or control group (usual care). The randomization will be performed in a 1:1 ratio, stratified by center and block balanced. The block size will not be communicated to the investigators.

This will be an open-label study. No investigator will have access to the randomization scheme during the course of the study.

6.4 STUDY INTERVENTION COMPLIANCE

During hospitalization, the follow-up of the treatment is ensured by the investigative team in charge of the patient who will record the date and time of the administrations. If the patient is discharged before day 7, the patient should be asked to note the date and time of each dose taken.

6.5 CONCOMITANT THERAPY

6.5.1 Auxiliary medication

In both the investigational and comparator treatment groups, patients will be treated according to routine practice.

Therefore, products will be prescribed in both groups and administered in accordance with routine care. They will not be provided by the Sponsor.

6.5.2 Authorized and prohibited treatments

The co-prescription of furosemide, prednisone and nitrates derivatives with the following drugs is not recommended for patients:

- Sildenafil, tadalafil or vardenafil
- Acetylsalicylic acid (in anti-inflammatory doses >= 1g per dose and/or >= 3g per day)
- Potent CYP3A inhibitors
- Mifamurtide
- Lithium
- Ototoxic medication (glycopeptides such as vancomycin and teicoplanin, aminoglycosides, organoplatins and loop diuretics)
- Hypokalaemic drugs (hypokalaemic diuretics, alone or in combination, stimulant laxatives, glucocorticoids, tetracosactide and amphotericin B (IV route).)
- Hyponatraemic drugs (diuretics, desmopressin, antidepressants inhibiting the reuptake of serotonin, carbamazepine and oxcarbazepine.).

6.5.3 Rescue Medicine

Aside from the study treatment, the management of the patient is at the discretion of the treating physician. If there is a formal indication for further steroid therapy, the prednisone treatment can be given in the control group and recorded in the CRF, and in both groups even after day 7. All treatments necessary for the proper management of the patient's state in the ED/hospital and subsequent hospitalization are authorized.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Several situations are possible:

- Temporary suspension of treatment: the investigator must document the reason for suspending and resuming the treatment in the participant's source file and the case report form (CRF)
- Premature discontinuation of treatment, but the participant remains enrolled in the study until the end of their participation
- Premature discontinuation of treatment and withdrawal from the study
- If, during the course of his/her participation in the study, the participant presents one of the following criteria, then the study treatment must be discontinued but the participant will continue to be monitored for the study.
    - Thrombo-embolism event
    - Fracture
    - Gastro-intestinal bleeding
    - altered consciousness, confusion or dementia, psychotic state,
    - vaccination, hypersensitivity reaction,
    - pregnancy, severe renal or hepatic impairment, or
    - uncontrolled hyperglycemia.

The investigator must:

- Document the reason(s)
- Collect the assessment criteria at the time of ending participation in the study, if the participant agrees
- Schedule a follow-up for the participant, particularly in case of a serious adverse event.

In the case of severe adverse events, the investigator must notify the sponsor and follow up the participant for 1 month following the premature discontinuation of treatment. The Sponsor will be notified immediately of any serious adverse event. The serious adverse event will be monitored until it is resolved.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- Participants may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.

If a participant withdraws consent, any data collected prior to the date of premature exit may still be used.

Participants are free to withdraw from participation in the study at any time upon request. The patient should be considered to have withdrawn consent only when the patient has withdrawn consent to further participate in any aspect of the study, including any further visits, assessments, or study-related contacts. If a patient fully withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information. The study intervention must be discontinued and no further assessments conducted. Information collected prior to withdrawal from the study will still be used. Information that has already been sent to the study Sponsor cannot be withdrawn. All biological material that has not been analyzed at the time of withdrawal must not be used. If the participant requests, previously retained samples will be destroyed to prevent further analysis. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up. However, if local regulations permit, the investigator will be asked to check public registries on a regular basis to obtain the survival status (dead or alive) of any patients who failed to complete the study.

In case of serious adverse events, see the corresponding section 8.3.6 for reporting requirements.

If a participant discontinues the study, this will in no way affect their usual care for their condition. In the event of serious adverse events following premature discontinuation of treatment see section 7.1.

Patients who are randomized in error may be withdrawn from the study and replaced (with assignment of new study identification number and new randomization). Patients randomized in error will not be included in the analyses.

Patients who are randomized and then withdraw or are withdrawn from the study will not be replaced. These patients will be included in analyses. Incomplete follow-up will be handled as censored observations in time-to-event analyses, and missing data will be handled through imputation as appropriate.

7.3 LOST TO FOLLOW-UP

If the participant cannot be located, the investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

8.1.1 C-reactive protein

C-reactive protein will be measured at 24 hours, 72 hours, and day 7.

8.1.2 Physical examination

A study physician will perform a physical examination including vital signs, weight, and a clinical HF assessment at Visits 1 (randomization), Visit 2 (24 hours' post-randomization (day 2)), Visit 3 (72 hours post-randomization (day 4)) or at discharge if earlier, Visit 4 (day 7), and Visit 5 (30 days post-randomization). To reduce variability and increase sensitivity to detect changes, these evaluations should be done at the same time of day if possible, in the same position(s), and, preferably, in the same setting and by the same assessor.

Vital signs will include temperature, pulse, respiratory rate, systolic and diastolic blood pressure and weight. Height will be measured at Visit 1. Vital signs recorded as part of routine standard of care during the admission and prior to inclusion are considered part of the medical history required to assess study eligibility. Systolic and diastolic blood pressure should be measured during follow up visits using an appropriately sized blood pressure cuff in both arms at least once, and the arm with the higher blood pressure used for all subsequent measurements. To reduce variability, body weight should be measured using the same scale throughout if possible.

The clinical HF assessment will include ratings of the following HF signs and symptoms:

Dyspnea on exertion / NYHA class:
Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
Class II: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
Class III: Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV: Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Orthopnea**:** Patient should be observed after being in the lowest recumbent position for 10 – 15 minutes or queried to determine the minimum number of "pillows" required to obtain/maintain comfort while supine:
0 = None
1 = 1 pillow (10 cm)
2 = 2 pillows (20 cm)
3 = > 30 degrees
Not evaluable: Examination could not be performed / result unobtainable. The patient is on mechanical ventilation for non-cardiac reasons, cannot lie flat due to body habitus or orthopedic restrictions.

Peripheral Edema**:** edema in any dependent area, including the lower extremities or the sacral region.
0: Complete absence of skin indentation with mild digital pressure in all dependent areas.
1+: Indentation of skin that resolves over 10–15 seconds.
2+: Indentation of skin is easily created with limited pressure and disappears slowly (15–30 seconds or more).
3+: Large areas of indentation easily produced and slow to resolve (> 30 seconds).

Rales:
No rales: No rales after clearing with cough.
Rales < 1/3: Moist or dry rales heard in lower 1/3 of one or both lung fields that persist after cough.
Rales 1/3–2/3: Moist or dry rales heard throughout the lower half to 2/3 of one or both lung fields.
Rales > 2/3: Moist or dry rales heard throughout both lung fields.

Jugular venous pulse (JVP) in centimeters as 5 + (the vertical distance from the top of the pulsation in jugular veins to the sternal angle of Louis). Assess with patient supine at ~ 45° off the horizontal until the jugular venous pulsation is visible half-way up the neck.
< 6 cm: Complete absence of discernable venous wave, even with hepatic compression.
6–10 cm: Venous wave detectable during expiration or complete respiratory cycle, less than 4 cm above clavicle (< 10 cm).
> 10 cm: Presence of venous wave throughout respiratory cycle sometimes ≥ 4 cm above clavicle and increased with hepatic compressions.
Not evaluable: Examination could not be performed/result unobtainable. Unable to determine due to patient's body build (habitus) or other reason.

8.1.3 Electrocardiography (ECG)

A standard 12-lead ECG is expected to have been obtained as part of routine standard of care.

8.1.4 Chest X-ray or lung ultrasound

Evidence of pulmonary congestion on chest X-ray or 2 or more B-lines on lung ultrasound is required for study eligibility.

8.1.5 Worsening heart failure

The physician will evaluate the occurrence of worsening heart failure in the preceding interval (i.e., at Visit 3, the occurrence of WHF between Visit 2 (24 hours post-randomization) and Visit 3 (72 hours post-randomization). The investigator will report all events of worsening signs and/or symptoms of heart failure occurring through day 31 as an adverse event. Worsening heart failure will be evaluated in two ways: (1) for the secondary endpoint, all adverse events of worsening heart failure will be included. (2) for the exploratory endpoints, worsening heart failure that occurs between 24 hours and 7 days after randomization, where both worsening signs and/or symptoms of HF and intensification of therapy for HF including up-titration of intravenous therapy, or mechanical ventilatory, renal, or circulatory support occurred will be included.

8.1.6 Other clinical outcomes

Deaths will be recorded through 90 days post-randomization. The primary cause will be recorded when possible. Every effort (consistent with all applicable laws and regulations) will be made to obtain vital status on all randomized subjects.

The length of stay in an intensive care unit (ICU) or other acute care unit and the total length of hospital stay will be recorded for the initial hospitalization and of each rehospitalization through 90 days following randomization. The primary reason for the readmission to the hospital will be recorded. A rehospitalization is defined as an unplanned overnight stay in the hospital, regardless of whether the patient was admitted.

8.1.7 Laboratory assessments

Blood samples (plasma) for central laboratory assessment will be taken at Visit 1 prior to randomization, at 72 hours and day 7 (± 1 day) as well as day 31. Samples will be collected in EDTA sample collection tubes and handled as described in the study's Laboratory Procedures manual. Sample aliquots will be stored frozen locally until shipped for longer-term storage and analysis. Unused samples will be discarded within 5 years after the study's completion.

Other lab assessments will be made according to local clinical practice. This should include at a minimum hemoglobin, WBC count, lymphocyte count, sodium, potassium, glucose, liver and kidney

function tests before randomization, day 7 (± 1 day), as well as day 31. Any assessments done at 24 hours (day 2) and/or 72 hours (day 3) should be recorded but are not required.

8.1.8 EQ-5D-5L questionnaire

The EQ-5D is a standardized instrument developed by the EuroQoL Group (www.euroqol.org) that measures health-related quality of life (The Euroqol Group 1990). The EQ-5D consists of two pages, which should take only a few minutes to complete (Oppe, Rabin et al. 2008). The first page asks the patient to indicate his/her health state for each of 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). The second page asks the patient to rate his/her health on a vertical visual analogue scale (EQ-VAS), where the endpoints are labeled "Best imaginable health state" at the top and "Worst imaginable health state" at the bottom. The 5-level EQ-5D version (EQ-5D-5L), introduced in 2009, increased the number of possible response levels to each health dimension from 3 to 5.

The patient will be asked to complete the EQ-5D-5L questionnaire at Visits 1 (randomization), Visit 4 (day 7), and Visit 5 (30 days post-randomization) in a quiet, private space prior to any invasive or demanding study or routine procedures, e.g., blood draws, by using the official linguistically validated translation of the EQ-5D-5L. See appendix in section 12.1 for sample English version (not to be used in the study).

8.2 SAFETY AND OTHER ASSESSMENTS

Safety will be assessed at each study visit. In addition to assessment of signs and symptoms during physical examination, safety will be assessed through local laboratory values obtained as standard of care and per protocol. The occurrence of any adverse events will also be elicited through non-directive questioning of the patient at each study visit and through recording of any event spontaneously reported by the patient or noted by the investigator.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 Definition of Adverse Events (AE)

Adverse event (AE) means any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A).

Adverse drug reactions (ADRs) include all noxious and unintended responses to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

An unexpected adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

8.3.2 Definition of Serious Adverse Event (SAE) or Adverse Drug Reaction

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening, NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect, or
- is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of

the other outcomes listed in the definition above. These events should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

8.3.3 Classification of an Adverse Event

8.3.3.1 Severity of Event

The following guidelines will be used to describe severity of each adverse event:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 Expectedness

The Medical Monitor will be responsible for assessing whether a suspected serious adverse reaction is expected or unexpected. A suspected serious adverse reaction will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 Time Period and Frequency for Event Assessment and Follow-Up

The Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until day 31 or the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

8.3.5 Adverse Event Reporting

The investigator must assess the seriousness of each adverse event and record all serious and non-serious adverse events in the case report form (CRF). The investigator must document serious adverse events as thoroughly as possible and provide a definitive medical diagnosis, if possible.

8.3.6 Serious Adverse Event Reporting

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC) and/or study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying the local competent authorities of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor will notify local competent authorities and all participating investigators of any new potential serious risks, from

clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

8.3.7 Events of Special Interest

As done in usual care, any secondary effect of steroids treatment will be assessed at every visit with a special attention to:

- Active infection
- Thrombo-embolism event
- Fracture
- Gastro-intestinal bleeding

The investigator must notify the sponsor without delay on the day the investigator becomes aware of the following adverse events, in the same manner and within the same deadline as for serious adverse events (see above).

- Thrombo-embolic event
- Gastro-intestinal bleeding

8.3.8 Reporting of Pregnancy

Any pregnancy that occurs following randomization through Day 31 should be reported to the Medical Monitor and to the Sponsor.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary statistical null hypothesis to be tested is that the mean change in CRP from inclusion to day 7 does not differ between patients randomized to prednisone therapy and those randomized to usual care. The alternative hypothesis is that the mean change in the two groups differ. Two-sided $p<0.05$ will be considered statistically significant, with a greater CRP reduction in the investigational arm considered superior.

9.2 SAMPLE SIZE DETERMINATION

Raess et all (2021) observed a 58% lower day 7 CRP level in patients with community-acquired pneumonia treated with 7 days of 50 mg/day prednisone (geometric mean 14.71, geom SD 2.47) than with placebo (geom mean 34.84, geom SD 2.98). Baseline CRP levels were similar in the two groups with geometric means (SDs) of 121.57 (2.77) and 124.58 (2.70) mg/L, in the active and placebo treatment groups respectively.

Sixty patients per group provides approximately 80% power to detect a 40% lower day 7 CRP level in the intervention (prednisone + routine care) group than in the control (routine care) group at the 2-sided 0.05 significance level assuming a common geometric standard deviation of 2.7237 (SD of logs 1.002). Power was estimated using a t-test, although groups will be compared with respect to the day 7 CRP level using MMRM as described below. CRP values will be log-transformed for analysis.

9.3 POPULATIONS FOR ANALYSES

Since the trial is a small pilot study, and a few inappropriately enrolled or treated patients can have a major effect on the findings, the main analysis will be performed in the per-protocol population. Sensitivity analyses on the main endpoint will be performed considering the intention-to-treat population.

Intention to treat population (ITT): all randomized patients, excluding patients randomized in error (e.g., non-existent patients or patients randomized and found to be ineligible before study treatment started) regardless of the strategy received by the patient. Patients will be analyzed according to the treatment to which they were assigned at randomization.

The per-protocol (PP) population is defined as all patients randomized (excluding patients randomized in error), without major protocol violations/deviations. Pre-defined major protocol violations/deviations are:

- Non-respect of eligibility criteria
- Non-respect of the allocated treatment

Major protocol deviation will be classified during a data review before final data base lock.

In case of consent withdrawal, only data collected before withdrawal will be used.

9.4 STATISTICAL ANALYSES

9.4.1 General Approach

Analysis will be performed by a statistician from the Data Coordinating Center using SAS® software (version 9.4 or updated version).

Continuous variables will be summarized using descriptive statistics, i.e. number of subjects, mean, standard deviation (SD), median, inter quartile range, minimum and maximum depending on the variable distribution. Categorical variables will be summarized by frequency and percentage.

The statistical analysis plan (SAP) will include a more technical and detailed description of the statistical analyses described in this section. It will be written before data base lock. In case of occurrence of such validated modifications after the SAP, a modified SAP would be issued. The original SAP as well as the modified SAP will be kept in the study files, with the justification for any modification. The SAP will prevail in case of any differences with planned analyses described in this protocol.

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

The primary endpoint of change in CRP level (CRP level measured at inclusion, day 2, day 4, day 7, and day 31) will be compared between treatment groups using an appropriate contrast at day 7 from a mixed model for repeated measures (MMRM) of post-inclusion changes in CRP that includes the effects of center, baseline CRP, treatment, visit, baseline CRP×visit and treatment×visit. CRP values will be log-transformed for analysis. Patients' available measures will be included in the model with no imputation for missing values. MMRM with a contrast may provide more power than a complete-case ANCOVA, and should include baseline covariates×time interactions to minimize bias.

9.4.3 Analysis of the Secondary Endpoint(s)

Treatment groups will be compared with respect to the occurrence of a WHF adverse event, or HF readmission, or death from any cause from randomization through day 91 with a log-rank test stratified by study center. The time to event will be calculated as the date of the first occurrence of any of the component events minus the date of randomization plus 1. If a patient has no component event by day 91, the time to event will be censored at the earlier of 90 days after randomization or the day of last available follow-up.

The changes in EQ-5D-5L index value and in EQ-VAS from randomization to day 7, will be compared between treatment groups using an appropriate contrast at day 7 from a mixed model for repeated measures (MMRM) for each outcome that includes the effects of the baseline value (EQ-5D-5L index or EQ-VAS as applicable), study center, treatment, visit, baseline value×visit and treatment×visit. EQ-5D index will be derived for each patient from the French value set. Patients who are missing a response due to death will be assigned the index value equivalent to death (0) and worst possible VAS score (0). The method assumes that missing data are missing at random (MAR) and the hypothetical treatment effect that is estimated is what would have been observed if all patients had continued on the assigned treatments for the full treatment period. Shifts in responses to each dimension from baseline to each time point will also be described.

9.4.4 Safety Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of adverse events with an onset after randomization through 30 days post-randomization will be tabulated by system organ class and preferred term. All adverse events, fatal adverse events, serious adverse events will be summarized by treatment group. Treatment-related adverse events are those that are considered by the investigator as potentially, probably, or definitely related to the study intervention.

9.4.5 Baseline Descriptive Statistics

A flow chart will be drawn according to CONSORT statement. Baseline characteristics of patients will be described overall and per group.

9.4.6 Planned Interim Analyses

No interim analysis is planned. The study will be terminated after all patients have been enrolled and followed according to the protocol assessments. Analysis will be performed at the end of the study after data review and data base lock.

9.4.7 Sub-Group Analyses

Although power to detect significant interactions may be limited, analyses examining the treatment effect on the primary and secondary endpoints by subgroups based on baseline characteristics will be performed for the following factors:

- Sex: male versus female
- Age: < 65 versus ≥ 65 years
- Baseline IL-6 : ≤ 13 pg/mL versus IL-6 > 13 pg/mL

9.4.8 Tabulation of Individual participant Data

No tabulation of individual participant data is planned.

9.4.9 Exploratory Analyses

The following exploratory endpoints will be assessed:

1. The composite of WHF, death, or hospital readmission for decompensated HF at day 31, where WHF is defined as worsening signs and/or symptoms of HF that require an intensification of intravenous therapy (including initiation or re-initiation or dose increase) for HF or mechanical ventilatory, renal or circulatory support (occurring between 24 hours after randomization and the earlier of discharge or day 7).
2. The composite of WHF, death, or hospital readmission for decompensated HF at day 91, where WHF is defined as worsening signs and/or symptoms of HF that require an intensification of intravenous therapy (including initiation or re-initiation or dose increase) for HF or mechanical ventilatory, renal or circulatory support (occurring between 24 hours after randomization and the earlier of discharge or day 7).
3. Changes in quality of life measured by the EQ-5D-5L from randomization to day 31.
4. Changes from randomization to day 7 in NYHA classification, orthopnea, peripheral edema, rales, jugular venous pulse, and body weight.
5. Death from any cause to days 31 and 91.
6. Readmission for HF or death to days 31 and 91.
7. HF readmission through days 31 and 91.
8. Requirement for treatment with intravenous vasopressors, inotropes, and/or mechanical ventilatory, renal or circulatory support or death from randomization through day 7 (“treatment failure”).
9. Changes from randomization to day 7 and to day 31, in biomarker levels including brain natriuretic peptide (BNP), NT-pro-BNP, creatinine and troponin.
10. Time to worsening heart failure through the earlier of day 7 or discharge.
11. Length of stay in ICU through 30 days following randomization

12. Length of initial hospitalization through 30 days following randomization
13. Days dead or in acute care (including all intensive acute care units) out of the first 30 days following randomization.
14. Days dead or in the hospital out of the first 30 days following randomization.
15. Hospital re-admission through days 31 and 91.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Informed Consent Process

10.1.1.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

10.1.1.2 Consent Procedures and Documentation

No interventional research involving human participants can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in ICH E6 Guideline for Good Clinical Practice.

A reflection period if needed is given to the individual between the time when he or she is informed and when he or she signs the consent form.

The person’s freely-given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study.

A copy of the information note and consent form, signed and dated by the research participant and by the principal investigator or the physician representing the investigator will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her consent as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

The participant may not enroll in another interventional study protocol involving human participants for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study. The participants can, however, participate in other non-interventional studies.

10.1.2 Study Discontinuation and Closure

The Sponsor can prematurely discontinue all or part of the study, temporarily or permanently, further to the recommendations of the Medical Monitor if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the treatment arms or if there is a discrepancy in the serious adverse reactions between the treatment arms, requiring a reassessment of the benefit-risk ratio for the study.

Similarly, the Sponsor or the Competent Authority may decide to prematurely discontinue the study due to unforeseen issues or new information about the product, in light of which the objectives of the study or clinical program are unlikely to be achieved.

The Sponsor reserves the right to permanently suspend enrolment at any time if it appears that the inclusion objectives are not met.

Patients already enrolled in the study at the time the study is prematurely discontinued will complete all study assessments through Day 91 as set forth in the protocol.

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor to the Competent Authority and to the Ethics Committees within a period of 15 days.

10.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their designates. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Ethics Committee (EC), regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant’s contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing EC, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Data Coordinating Center at Momentum Research, Inc. This will not include the participant’s contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the Data Coordinating Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Data Coordinating Center.

10.1.4 Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored at the Data Coordinating Center. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Heart Initiative or its designee, for use by other researchers including those outside of the study.

During the study the sample collected will be stored at the local investigational sites before being sent to the laboratory of Inserm UMRS942 - Hôpital Lariboisière, Secteur Violet, Porte 5, Bâtiment Viggo Petersen, 2e étage, 41, boulevard de la Chapelle, 75010 Paris for storage and biomarkers measures. At the end of the study, the samples will be kept at INSERM UMRS 942 for a period of up to 5 years, after which the samples will be destroyed.

At the end of the study, the samples may be used for further analysis not described in the initial protocol but which may be useful for investigation of the condition of heart failure in light of advances in scientific knowledge, provided the participant is informed and does not oppose this, as stated in the information note/consent form.

Type of sample	**Quantity**	**Storage location**	**Supervisor of the sample collection**	**Purpose of the sample collection**	**Storage duration**	**End use/Future**
Blood for plasma collection **EDTA Tube**	20 mL of blood	Laboratory INSERM UMRS 942	Pr Alexandre Mebazaa	Analysis of biomarkers of congestion, inflammation and renal function	5 years	Destruction after 5 years of storage

10.1.5 Key Roles and Study Governance

The contact information for the study's Principal Investigator and the Medical Monitor are given below.

Principal Investigator	**Medical Monitor**
Yonathan Freund, MD, PhD	Gad Cotter, MD
Emergency Department, Hôpital Universitaire Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris (AP-HP)	Momentum Research, Inc.
83 boulevard de l'Hôpital, 75013 Paris, France	1426 NC Highway 54, Suite B Durham, NC 27713 USA
+33 6 63 54 90 17	+1 919 599 0949
yonathanfreund@gmail.com	gadcotter@momentum-research.com

10.1.6 Safety Oversight

Safety oversight will be the responsibility of the Medical Monitor.

10.1.7 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Monitoring for this study will be performed by representatives of the Heart Initiative. Both on-site and centralized monitoring will be employed. Details of clinical site monitoring are documented in the Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

Independent audits may be conducted by representatives of Heart Initiative to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

10.1.8 Quality Assurance and Quality Control

Each clinical site will manage the internal quality of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 Data Handling and Record Keeping

10.1.9.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Any hardcopies of study visit worksheets should be maintained as source documents. Data recorded in the case report form (CRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into an Electronic Data Capture (EDC) system managed by the Data Coordinating Center. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

10.1.9.2 Study Records Retention

Specific documents for an interventional study involving human participants concerning a medicinal product for human use will be archived by the investigator and the sponsor for 15 years after the end of the research. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site

staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within the time frame deemed necessary by the regulatory authorities in the country and region the site resides in working days of identification of the protocol deviation. All deviations must be addressed in study source documents, and reported to the monitor and the Data Coordinating Center. Protocol deviations must be sent to the reviewing Ethics Committee (EC) per their policies. The site investigator is responsible for knowing and adhering to the reviewing EC requirements.

10.1.11 Publication and Data Sharing Policy

This trial will be registered in a clinical trials registry, and results information from this trial will be submitted to the registry. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 1 year after publication of the main manuscript by contacting the Heart Initiative.

Investigators will not publish study results from their institution prior to publication of the main manuscript for the study.

10.1.12 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse Event
AHF	Acute heart failure
ANCOVA	Analysis of Covariance
BIPAP	Bilevel positive airway pressure
CMP	Clinical Monitoring Plan
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CRF	Case Report Form
CRP	C-reactive protein
CRT	Cardiac resynchronization therapy
CYP3A	Cytochrome P450, family 3, subfamily A
DCC	Data Coordinating Center
EC	Ethics Committee
ECG	Electrocardiogram
ED	Emergency department
eGFR	Estimated glomerular filtration rate
FEV1	Forced expiratory volume in the first second

GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HF	Heart failure
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IL-6	Interleukin-6
ITT	Intention-To-Treat
IV	Intravenous
JVP	Jugular venous pulse
LSMEANS	Least-squares Means
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
MOP	Manual of Procedures
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PP	Per protocol
PTCI	Percutaneous transluminal coronary intervention
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
Tn	Troponin
VAS	Visual analog scale
WBC	White blood cell
WHF	Worsening heart failure

10.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	13Jun2023	N/A	Original version
2.0	5Jan2024	Amendment 1	Protocol amended primarily to change the secondary endpoint to include WHF events using a less stringent definition over a longer timeframe in order to increase study power for this small pilot study and to modify the planned statistical analyses. No modifications to planned study size, study eligibility criteria, or study procedures were made.

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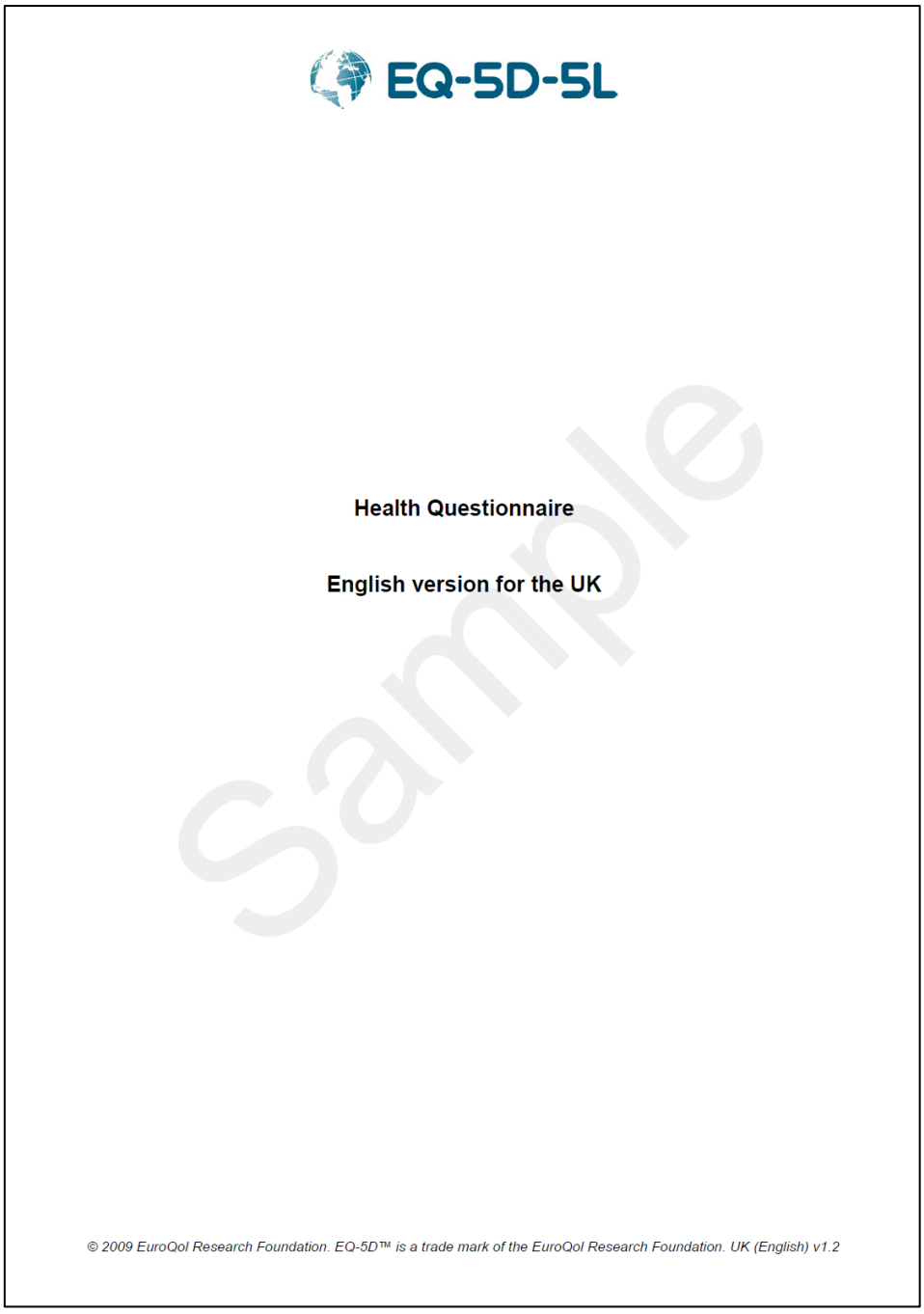
12 APPENDIX

12.1 EQ-5D SAMPLE UK ENGLISH VERSION



Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

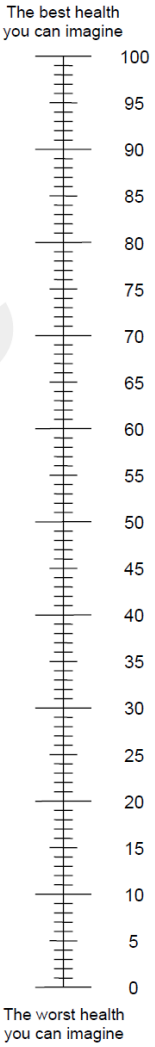
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3