Safety, Tolerability and efficacy of Rapid Optimization, helped by NT-proBNP testinG, of Heart Failure therapies

STRONG-HF

Protocol Identifying Number: CHF201701

Trial Registry and Number: ClinicalTrials.gov NCT03412201

EudraCT Number: 2018-000486-37

Sponsor:
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Version Number: 3.0

11 January 2021

Protocol Signature Page

Protocol Title: Safety, Tolerability and efficacy of Rapid Optimization, helped by NT-proBNPtestinG, of Heart Failure therapies (STRONG-HF)

Protocol Version/ Date: Version 3.0; 11 January 2021

Sponsor Name: Heart Initiative

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:

Summary of Changes from Version 2 to Version 3:

Affected Section(s)	Summary of Revisions Made	Rationale
All	Version number, date changed throughout to reflect amended protocol.	N/A
Title page, Protocol Signature Page, 10.1.5.2	Updated Sponsor's address and Medical Monitor's phone number.	Sponsor's address and Medical Monitor's phone number have changed.
Title page, 1.1, 1.3, 2.2, 2.3.1, 4.1, 4.2, 6.1.2, 8.2.6.1, 9.4.7, 9.4.9.5	Removed GDF-15 and references to its measurement.	Due to logistical issues, supplies for the testing of GDF-15 were largely unavailable to participating centers. Therefore, the measurement of GDF-15 has been removed from the protocol.
1.1, 1.2, 1.3, 4.1, 5.1, 5.2, 6.1.1, 6.1.2, 6.4, 8.2.5, 8.2.6.1, 8.2.6.2	Clarified timing of randomization relative to hospital discharge from "1-2 days before" to "within 2 days before".	Randomization on the day of discharge is acceptable. Thus, the timing was clarified to include the day of discharge itself.
1.1, 1.2, 3.0, 9.1, 9.2, 9.4.2, 9.4.3, 9.4.7, 9.4.9	Primary objective and endpoint revised to 180-day all-cause mortality or heart failure readmission.	An interim futility analysis was performed when 519 patients had completed Day 90 follow-up and 353 patients for whom 180-day follow-up was expected had completed Day 180 follow-up (or would have completed had they not discontinued the study or died). Conditional power calculations suggested that the study as it was designed had insufficient power to address the question of potential benefit of high intensity care on outcomes. To increase power the primary endpoint has been revised to 180-day all-cause death or HF rehospitalization, and the sample size increased accordingly. Analogous to the use of a weighted prior distribution in Bayesian analysis, the primary analysis will down-weight the interim 'hypothesis-generating' result in the initial cohort of patients who

		were included in the interim analysis of 180-day outcomes.
1.1, 3.0, 9.4.3	Secondary objectives and endpoints revised.	Secondary objectives and endpoints have been revised to include change in quality of life, 180-day all-cause mortality, and the former primary composite endpoint of 90-day all-cause mortality or HF readmission.
1.1, 9.4.9	Other endpoints revised to reflect changes to the secondary endpoints, and to add a hierarchical composite outcome.	Additional endpoints now include components of the primary and secondary composite clinical outcomes. The exploratory hierarchical composite outcome incorporates clinical outcomes (death and HF readmission) as well as changes in patient-reported quality of life at day 90. Changes in markers of congestion were moved from safety to efficacy.
1.1, 4.1, 6.3	Total enrollment increased from 900 to 1800 patients.	Randomization of 1800 patients, as well as movement of the primary endpoint from 90 to 180 days, will increase the power of the study to address the hypothesis of benefit of high intensity care on clinical outcomes.
1.1	Recruitment updated from expected 30 months to 60 months.	Enrollment of increased number of patients requires additional time.
1.1, 5.2, 6.1.1, 8.2.3	Cap on number of patients with a history of atrial fibrillation or flutter or with atrial fibrillation/flutter present at Screening eliminated.	The cap had been increased through a Note to File to 350 because of severe limitations in screening and enrollment resulting from Covid-19 restrictions. The cap has been dropped because of the resulting limitation on enrollment.
1.1	List of participating sites updated.	Description of sites updated to reflect where enrollment will occur.
1.1, 6.1.3	Characterization of the 90-day visit as the “last study visit” for randomized patients eliminated, and emphasis on 180-day contact for randomized patients added.	Randomized patients, in both the high intensity care and usual care groups, will be followed through 180 days post-randomization.

1.1, 9.1, 9.2, 9.4.2, 9.4.7	Statistical analysis plan, power calculations, and subgroup analysis plan revised to reflect new primary endpoint.	The difference between groups regarding the estimated rate of death or HF readmission at 180 days will a weighted average of the result in the initial cohort of patients who were included in the interim analysis of 180-day outcomes and subsequently enrolled patients. With total enrollment of 1800 patients and down-weighting the initial result by half its sample size, the study will have approximately 89% power to detect a difference in event rates of 14% versus 20% at the two-sided 0.05 significance level.
9.4.3, 9.4.4, 9.4.9	Statistical analysis plan revised to reflect new secondary and exploratory endpoints, and to detail the analysis of vital signs and to add the analysis of laboratory evaluations to the safety analyses.	The analysis plan has been updated to reflect the new classification of endpoints as secondary and exploratory. Clinical outcomes will be compared between treatment groups with methodology analogous to that used for the primary efficacy endpoint. A new hierarchical composite outcome was added as an exploratory endpoint. Alpha will be controlled through sequential testing of the secondary endpoints.
1.1, 4.1, 9.4.6	A futility analysis after enrollment of 1300 patients added.	Enrollment may be curtailed if the conditional power for the final result is very low.
5.4, 8.2.8, 8.3.4	Clarified minimal information for screen failures to be reported in the CRF.	Information required to provide patient accountability information for screen failures includes only demography, screen failure details and eligibility criteria. Information on SAEs between informed consent and screen failure determination is not required for this purpose.
1.3, 8.2.8, 8.3.4	Clarification of the reporting period for non-serious adverse events. Adverse events with an onset after informed consent through Day 90 for randomized patients will be recorded. All serious AEs with an onset from informed	Because the timing of Visit 7 may vary, the reporting period was clarified to refer to the study day post-randomization for randomized patients.

	consent through the date of screen failure determination for Screen Failures and through Day 90 for randomized patients will be recorded.	
6.1.1	The optimal (full) dose of spironolactone updated from 25 mg q.d. to 50 mg q.d. The half daily dose updated from 25 mg q2D to 25 mg q.d. accordingly.	The protocol's optimal dose has been revised to be consistent with the target dose for spironolactone included in the *2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure*.
6.1.2	Clarified the "target therapy dose" immediately following randomization.	The initial "target" dose of oral HF therapies immediately following randomization in the high intensity care arm is half the maximal recommended dose. This was made explicit to avoid confusion. Up-titration to full optimal doses occurs ideally at 2 weeks following randomization.
6.1.2	Recommendations to consider treatment with SGLT inhibitors and IV ferric carboxymaltose added.	Results of recent studies suggest that SGLT2 inhibitors are effective in reducing risk of clinical outcomes in patients with heart failure. IV ferric carboxymaltose was recommended in the 2016 ESC guidelines in HF patients with iron deficiency; results of recently completed trials strengthen this recommendation.
6.5	Clarified that medical procedures and non-drug therapies should be recorded in the patient's medical record.	Only major cardiovascular and non-cardiovascular classes of medications are to be recorded in the case report form.
7.2	Clarified the use of data and biological specimens following withdrawal from the study.	The text has been updated to reflect the wording in the informed consent.
9.3, 9.4.5	Analyses limited to the FAS (modified intent-to-treat) population.	Given the nature of the study, where the usual care group is seen less frequently than the high intensity care group, the potential biases introduced through the reclassification of treatment group for the safety set and the selection of a per protocol subset are unclear. Thus, efficacy and safety

		analyses will be conducted only the FAS. The FAS includes randomized patients, excludes only patients randomized in error, and includes patients in the their assigned treatment groups for analysis.
10.1.5.3	Frequency of Executive Committee meetings revised.	The Executive Committee cannot commit to monthly meetings. The committee will meet periodically throughout the study. The Medical Monitor and Data and Safety Monitoring Board are monitoring patient safety continuously, and the study's Principal Investigator is regularly updated.
10.3	Protocol amendment history updated.	The protocol amendment history has been updated to include Amendment 1 of the protocol, which was implemented in selected study centers.
11.0	Additional references added.	References added reflect revised statistical methodology to be employed.

Summary of Changes from Version 1 to Version 2:

Affected Section(s)	**Summary of Revisions Made**	**Rationale**
All	Version number, date changed throughout to reflect amended protocol.	N/A
Title page	Added EudraCT registration	The trial has been registered in EudraCT.
Protocol Signature Page	Left investigator name, signature, and date blank.	The page is to be signed by each participating site principal investigator.

1.1, 1.2, 1.3, 4.1, 8.1.1, 9.4.3.2	Added follow-up contact at 180 days after randomization to assess safety (vital status and hospitalizations) and medications.	Following implementation of the high-intensity strategy during the early 'vulnerable phase' post-discharge for AHF, the longer-term safety and potential benefit will be evaluated.
1.1, 1.3, 3.0, 8.1.1, 9.1, 9.2, 9.4.2, 9.4.3, 9.4.7, 9.4.9	Primary objective and endpoint revised to include all-cause death rather than cardiovascular death. Secondary objectives and endpoints revised	Although the cause of death will not be adjudicated, the vast majority of deaths in the first 90 days following discharge have been cardiovascular in other studies – primary and secondary outcomes have thus been revised to include all-cause rather than CV death. Change in NT-proBNP was elevated from an exploratory to a secondary endpoint as an additional marker of safety and potential efficacy.
1.1, 1.3, 5.1	Revised inclusion criterion # 1 from hospital admission within 24-48 hours prior to screening to within 72 hours prior to screening.	Longer time window allows for enrollment by study staff of patients admitted on Fridays or during public holidays.
1.1, 5.1, 6.1.1	Revised inclusion criterion # 5 from eligibility based on < ½ optimal doses of certain oral HF medications to ≤ ½ optimal doses.	To clarify that prescribed doses exactly = to ½ the optimal dose of these medications will meet the inclusion criterion.
1.1, 4.1	Participating geographic regions and countries and maximum number of sites updated.	The study has been expanded to geographic regions other than Europe.
1.1	Recruitment updated from expected 18 months to 30 months.	Enrollment in the study slower than anticipated.
3.0	Left ventricular ejection fraction categories updated from ≤ and ≥ 40% to ≤ 40 and > 40%.	For consistency throughout the protocol.
6.1	Half daily dose of lisinopril changed from 16.5 to 17.5 mg.	Typographical error correction.
8.2.6.2	Revised reference to "Laboratory Manual" to "Laboratory Procedures Manual"	Change was made to be consistent with the name of the document employed.

8.3.2	Addition of definition of hospitalizations and hospitalization prolongations that do not qualify as SAEs.	Clarification that planned or routine hospital admissions or routine prolonged hospital stays do not constitute SAEs.

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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:	Safety, Tolerability and efficacy of Rapid Optimization, helped by NT-proBNP testinG, of Heart Failure therapies (STRONG-HF)
Study Description:	STRONG-HF is a multicenter, randomized, parallel group study designed to evaluate the efficacy and safety of up-titration of standard of care medical therapy including beta-blockers; ACEi, ARB or ARNi; and MRAs, on morbidity and mortality when initiated and up-titrated early during hospitalization for acute heart failure (AHF). Optimal safety conditions will allow physicians to introduce and/or continue oral HF therapies during this "vulnerable phase" in acute heart failure (AHF) patients. Patients admitted for AHF with clinical signs of congestion and elevated circulating NT-proBNP and who are not treated with optimal doses of oral HF therapies within 2 days before hospital discharge for AHF and who are hemodynamically stable will be randomized in a 1:1 ratio to either usual care (named "usual care" arm) or intensification of treatment with beta-blockers, and ACEi (or ARB) or ARNi and a MRA (named "high intensity care" arm). In the latter arm, repeated assessments of clinical signs and symptoms of heart failure, routine clinical laboratory measures including potassium, sodium, and creatinine as well as biomarkers including NT-ProBNP will foster, encourage and ensure the safety of the optimization of oral heart failure therapies. Patients will be followed through 90 days from randomization. AHF patients who were screened but did not meet inclusion criteria, including low circulating NT-proBNP at visit 2, will also be followed for 90-day outcome. Randomized patients will be contacted at 180 days from randomization to assess vital status, occurrence of rehospitalizations, and oral HF medications.
Objectives:	Primary Objective: to assess the effects of optimization of medical therapy with beta-blocker; ACEi, ARB or ARNi; and MRAs on 180-day all-cause

mortality or heart failure readmission in patients admitted with acute heart failure and clinical and biological signs of congestion.

Secondary Objectives: The secondary objectives are to assess the effect of such intervention on change in quality of life (QoL) as measured by the EQ-5D questionnaire, 180-day all-cause mortality, and 90-day all-cause mortality or heart failure readmission.

Endpoints:

Primary Endpoint: 180-day all-cause mortality or HF readmission

Secondary Endpoints:

1. Change in quality of life measured by the EQ-5D questionnaire from randomization to day 90
2. 180-day all-cause mortality
3. 90-day all-cause mortality or heart failure readmission

Other endpoints: include 180-day and 90-day cardiovascular (CV) mortality; 90-day all-cause mortality; 180-day and 90-day HF readmission; a Finklestein-Schoenfeld hierarchical composite endpoint comprising death, HF readmissions, and change in EQ-VAS at 90 days; changes in NT-proBNP from randomization to day 90; changes in other biomarkers (TBD); and changes in weight and signs and symptoms of congestion. Changes in the primary and secondary endpoints will be examined in pre-determined subgroups including Left Ventricular Ejection Fraction ≤ or > 40%. Pharmacoeconomics analyses may also be performed.

Study Population:

1800 male or female patients 18 to 85 years of age admitted for AHF with clinical signs of congestion and elevated circulating NT-proBNP; who are not currently treated with target doses of oral beta-blockers, ACEi (or ARB if intolerant to ACEi) or ARNi, and MRA within 2 days before hospital discharge for AHF, and are hemodynamically stable. Eligible patients will be randomized to usual vs high intensity care within 2 days of discharge (visit 2).

<u>Inclusion criteria</u>

1. Hospital admission within the 72 hours prior to Screening for acute heart failure with dyspnea at rest and pulmonary congestion on chest X-ray, and other signs and/or symptoms of heart failure such as edema and/or positive rales on auscultation.
2. All measures within 24 hours prior to Randomization of systolic blood pressure ≥ 100 mmHg, and of heart rate ≥ 60 bpm.
3. All measures within 24 hours prior to Randomization of serum potassium ≤ 5.0 mEq/L (mmol/L).
4. Biomarker criteria for persistent congestion:
    a. At Screening, NT-proBNP > 2,500 pg/mL.
    b. At the time of Randomization (within 2 days prior to discharge), NT-proBNP > 1,500 pg/mL (to ensure the persistence of congestion) that has decreased by more than 10% compared to Screening (to ensure the acuity of the index episode).

5. At 1 week prior to admission, at Screening, and at Visit 2 (just prior to Randomization) either (a) ≤ ½ the optimal dose of ACEi/ARB/ARNi (see ***Table***) prescribed, no beta-blocker prescribed, and ≤ ½ the optimal dose of MRA prescribed or (b) no ACEi/ARB/ARNi prescribed, ≤ ½ the optimal dose of beta-blocker prescribed, and ≤ ½ the optimal dose of MRA prescribed.
6. Written informed consent to participate in the study.

Exclusion criteria

1. Age < 18 or > 85 years.
2. Clearly documented intolerance to high doses of beta-blockers.
3. Clearly documented intolerance to high doses of RAS blockers (both ACEi and ARB).
4. Mechanical ventilation (not including CPAP/BIPAP) in the 24 hours prior to Screening.
5. Significant pulmonary disease contributing substantially to the patients' dyspnea such as FEV1< 1 liter or need for chronic systemic or nonsystemic steroid therapy, or any kind of primary right heart failure such as primary pulmonary hypertension or recurrent pulmonary embolism.
6. 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 Screening.
7. 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.
8. Uncorrected thyroid disease, active myocarditis, or known amyloid or hypertrophic obstructive cardiomyopathy.
9. History of heart transplant or on a transplant list, or using or planned to be implanted with a ventricular assist device.
10. Sustained ventricular arrhythmia with syncopal episodes within the 3 months prior to screening that is untreated.
11. 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.

12. Active infection at any time during the AHF hospitalization prior to Randomization based on abnormal temperature and elevated WBC or need for intravenous antibiotics.
13. Stroke or TIA within the 3 months prior to Screening.
14. Primary liver disease considered to be life threatening.
15. Renal disease or eGFR < 30 mL/min/1.73m^2 (as estimated by the simplified MDRD formula) at Screening or history of dialysis.
16. Psychiatric or neurological disorder, cirrhosis, or active malignancy leading to a life expectancy < 6 months.
17. Prior (defined as less than 30 days from screening) or current enrollment in a CHF trial or participation in an investigational drug or device study within the 30 days prior to screening
18. Discharge for the AHF hospitalization anticipated to be > 14 days from admission, or to a long-term care facility. Randomization must occur within 12 days following admission and at within 2 days prior to anticipated discharge.
19. Inability to comply with all study requirements, due to major co-morbidities, social or financial issues, or a history of noncompliance with medical regimens, that might compromise the patient's ability to understand and/or comply with the protocol instructions or follow-up procedures
20. Pregnant or nursing (lactating) women.

AHF patients who were screened but did not meet inclusion criteria, including lower circulating NT-proBNP at visit 2, will also be followed for 90-day outcome (death and readmissions).

Phase: N/A

Description of Sites/Facilities Enrolling Participants: The study will be recruited in up to 90 sites, with experienced investigators, from countries in Europe, Russia South and North America, and Africa.

Description of Study Interventions: In the "usual care" arm the patient will be followed by the patient's cardiologist and/or general physician as per the usual care practiced in the country and specific community. The patient's next contact with the investigator will be at the 90-day visit.

The "high intensity care" arm will follow an algorithm combining optimization of oral HF therapies and frequent visits, including circulating NT-proBNP measures, to assess congestion. The first dose adjustment occurs just following randomization at the Randomization visit (Visit 2, within 2 days before discharge), when patients will be prescribed medical therapy with beta-blockers, ACEi (or ARB if intolerant to ACEi) or ARNi and MRA adjusted to at ≥ ½ the optimal doses for all three classes of medications.

These patients will then be assessed by the study team at 1 (visit 3, safety), 2 (visit 4, safety and up-titration to optimal doses), 3 (visit 5, safety), and 6 weeks (visit 6, safety) following randomization.

Safety and tolerability will be assessed at visits 3 to 6 by full physical examination, and laboratory assessments of NT-proBNP, sodium, potassium, kidney function measures, glucose and hemoglobin. Safety and tolerability will be assessed at visit 3 (1 week following randomization). At visit 4 (2 weeks following randomization), up-titration to full optimal doses of beta-blockers, ACEi/ARB/ARNi, and a MRA should be performed given adequate safety. Clinical assessments and follow-up measures of NT-proBNP will guide the safety of up-titrations of oral HF medications and optimal dosage of diuretics. Investigators will assess congestion, and increase diuretics as needed. ACEi/ARB/ARNi and or MRAs will not be up-titrated if the systolic blood pressure is < 95 mmHg, serum potassium > 5.0 mmol/L or eGFR is < 30 ml/min/1.73m^2. Beta-blockers will not be up-titrated if heart rate < 55 bpm or systolic BP is < 95 mmHg. If the NT-proBNP level is >10% higher than the pre-discharge level physicians should consider not up-titrating beta-blockers and consider increasing diuretics.

Safety and tolerability will be assessed again at Visit 5 (3 weeks follow-up) and visit 6 (6 weeks follow-up). Additional visits will be done at 1 week following any up-titration to assess safety and tolerability.

All randomized patients, and screen failures, will be followed at 90 days for the occurrence of hospital re-admissions or death. The occurrence of adverse events and outpatient visits through 90 days will be recorded for all randomized patients. Randomized patients will be contacted again at 180 days following randomization to assess vital status, rehospitalizations, and use of oral HF medications.

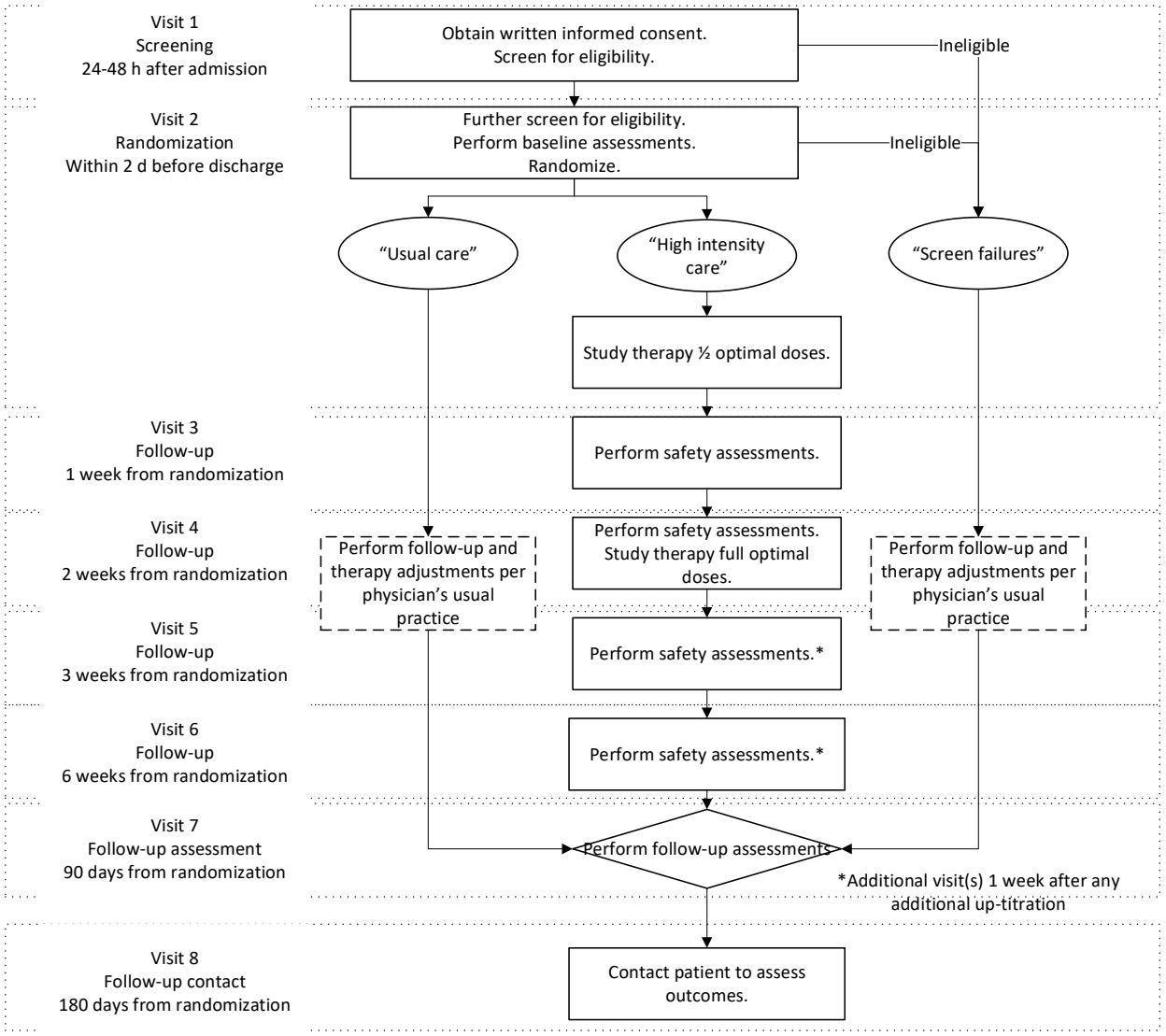
Statistical Considerations:

An interim futility analysis was performed when 519 patients had completed Day 90 follow-up (or would have completed if they had not died or discontinued the study) and 353 patients for whom 180-day follow-up was expected had completed Day 180 follow-up (or would have completed had they not discontinued the study or died). Conditional power calculations suggested that the study as it was designed had insufficient power to address the question of potential benefit of high intensity care on outcomes. To increase power the primary endpoint has been revised to 180-day all-cause death or HF rehospitalization, and the sample size increased accordingly. Analogous to use of a weighted prior distribution in Bayesian analyses, the primary analysis will include results from both the initial cohort that gave rise to the interim 'hypothesis-generating' 180-day result and the cohort of patients enrolled subsequently but down-weighting the result in the initial cohort.

The primary efficacy analysis of the primary outcome (180-day all-cause mortality or HF readmission) will include randomized patients with the exception of those patients who were randomized in error, and will exclude patients where 180-day follow-up is not expected. Patients will be analyzed according to the treatment to which they were assigned at randomization.

	The two treatment groups will be compared at the two-sided 5% significance level (equivalent to a one-sided 2.5% significance level) with respect to the difference in the cumulative rates of the primary endpoint at 180 days. A weighted average of the differences in cumulative event rates for the initial and subsequent cohorts, and its associated variance will be derived from Kaplan-Meier estimates adjusted for randomization strata (HFrEF v. HFmrEF/HFpEF and country) using Mantel-Haenszel weights and their associated standard errors. The primary analysis will weight the result in the initial cohort by half its sample size. Treatment groups will be compared using a chi-square statistic with 1 df derived from the weighted average difference and associated variance. Assuming that 20% of patients in the "usual care" group die or are re-admitted for HF within 180 days, enrollment of 1800 total patients provides approximately 89% power for the chi-square test to detect a difference of 6% (14% versus 20%), and approximately 75% power to detect a difference of 5% (15% versus 20%), at the two-sided 0.05 significance level. An interim futility analysis is planned when approximately 1300 patients have 180-day follow-up available. It is not intended to stop the trial early on the basis of superior efficacy.
Study Duration:	Recruitment is expected to continue for 60 months following the first patient visit, followed by approximately 6 months follow up for last patient enrolled and 2 months of close up.
Participant Duration:	Each patient's participation will be approximately 6 months.

1.2 SCHEMA


Visit 1
Screening
24-48 h after admission
Obtain written informed consent.
Screen for eligibility.
Ineligible
Visit 2
Randomization
Within 2 d before discharge
Further screen for eligibility.
Perform baseline assessments.
Randomize.
Ineligible
"Usual care"
"High intensity care"
"Screen failures"
Study therapy ½ optimal doses.
Visit 3
Follow-up
1 week from randomization
Perform safety assessments.
Visit 4
Follow-up
2 weeks from randomization
Perform follow-up and therapy adjustments per physician's usual practice
Perform safety assessments.
Study therapy full optimal doses.
Perform follow-up and therapy adjustments per physician's usual practice
Visit 5
Follow-up
3 weeks from randomization
Perform safety assessments.*
Visit 6
Follow-up
6 weeks from randomization
Perform safety assessments.*
Visit 7
Follow-up assessment
90 days from randomization
Perform follow-up assessments
*Additional visit(s) 1 week after any additional up-titration
Visit 8
Follow-up contact
180 days from randomization
Contact patient to assess outcomes.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Assessment	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	Screening ≤ 72h after admission	Randomization within 2d before discharge	Week 1 1 week after randomization§	Week 2 2 weeks after randomization	Week 3 3 weeks after randomization	Week 6 6 weeks after randomization	Day 90 90 days after randomization	Day 180 180 days after randomization
Eligibility	X							
Medical history	X							
Chest X-ray*	X							
ECG*	X							
NT-proBNP	X	X	X (high†)	X (high)	X (high)	X (high)	X	
Local labs including Hgb, serum sodium, glucose, potassium and kidney function measures	X	X	X (high)	X (high)	X (high)	X (high)	X	
Physical exam including vital signs and clinical HF assessment	X	X	X (high)	X (high)	X (high)	X (high)	X	
Medications	X	X	X (high)	X (high)	X (high)	X (high)	X	X
Randomization		X						
Study therapy optimization		X (high-half‡)		X (high-full‡)	X (high-full)	X (high-full)	X	
Adverse events		←--------	----------X----------→					
Clinical outcomes		←--------	----------X----------					----→
EQ-5D		X					X	
Biobanking samples		X					X	

*Non-study-related procedure expected as standard of care for acute heart failure and required to assess eligibility. Echocardiogram should have been performed within 6 months prior to Screening.

†"high" = high intensity care arm only

‡Following randomization, beta-blocker, ACEi (or ARB if intolerant to ACEi) or ARNi, and MRA at ½ optimal dose at Visit 2 and at full optimal dose at Visit 4.

§Additional visit(s) to assess safety and tolerability to be performed 1 week following any up-titration.

2 INTRODUCTION

2.1 STUDY RATIONALE

No randomized controlled trial (RCT) has shown benefits in either morbidity or mortality in acute heart failure. RCTs have mostly tested intravenous short-acting therapies (vasodilators or inotropes) in the initial phase after admission for acute heart failure and examined long-term outcome. No RCT has examined the potential effects of rapid up-titration of evidence based therapies – beta-blockers and RAAS inhibitors during the pre-discharge and immediate post discharge period in patients admitted for AHF.

2.2 BACKGROUND

By contrast to the lack of benefits of intravenous therapies in AHF, several classes of oral heart failure medications, including beta-blockers, ACEi, ARB or ARNi and MRA, have shown benefit on long-term outcome in chronic stable heart failure patients (Ponikowski, Voors et al. 2016).

However, a large part of AHF patients are not adequately followed and undertreated during the "vulnerable phase" - the few months following discharge from AHF. This is associated with marked excess of hospital readmission and of death. Potential reasons of under treatment after discharge include: 1) lack of RCT on post-discharge follow-up, 2) lack of recommendations on number of visits and ways to achieve optimal therapies or 3) management by non-heart failure specialists.

Guidelines of Joint American Heart Association and American College of Cardiology (published in 2013, updated in 2017,(Yancy, Jessup et al. 2013; Yancy, Jessup et al. 2017) and HFSA (published in 2016)(Yancy, Jessup et al. 2016) give no indication on the number of visits after hospital discharge from an AHF episode. European Society of Cardiology (2016) recommends "a follow-up plan after discharge" and that "patients should preferably be seen by GP within a week of discharge, if feasible"; no indications were given for later visit(s)(Ponikowski, Voors et al. 2016).

The other major issue is that guidelines do not indicate what to do during the post-discharge visit. In fact, a rapid optimization of oral HF therapies often raises safety concerns by treating physicians. Though, no excess morbidity or mortality was shown by rapid optimization of oral HF therapies, physicians are afraid that beta-blockers and/or ACEi may induce hypotension or hypokalemia, worsen renal function, or worsen congestion and result in a novel episode of AHF.

Recently, we and others demonstrated that oral heart failure therapies, especially the combination of beta-blockers and ACEi are associated with a rapid benefit on survival when given at discharge from AHF. This benefit on outcome is seen in all range of left ventricular ejection fraction (Gayat, Arrigo et al. 2017) . In summary, clear and practical indications on ways to optimize "safely" oral heart failure medications during the "vulnerable" phase is urgently needed.

We propose combining immediate optimization of oral HF therapies and continuous visits to assess persistent improvement in congestion. Thus, in the "high intensity care" arm STRONG-HF provides the best conditions for physicians 1) to optimize oral HF therapies within 2 weeks after hospital discharge, while 2) monitoring safety by continuous measures of cardiovascular biomarkers during the "vulnerable phase", in the AHF patients.

To do so, STRONG-HF will select, during the index hospitalization and based on high circulating NT-proBNP, AHF patients with the greater need of oral HF therapies. Circulating NT-proBNP will be further measured, repeatedly, during the post-discharge "vulnerable" phase to assess the safety of the optimization of oral HF therapies and specifically the continuous improvement of congestion.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Patient assigned to the "high intensity care" arm will be treated with oral HF medications with an aim to optimize medical therapy to include beta-blockers, blockers of the renin aldosterone angiotensin system and mineralocorticoid receptor antagonists at optimal doses recommended in current ESC guidelines (Ponikowski, Voors et al. 2016). The risks for each specific medication are detailed in prescribing information (package insert) supplied by manufacturers. The only potential risk to the patient is that during the up-titration of the above mentioned medications patients may experience adverse events known to be associated with those medications. However, these adverse events are part of the usual course of heart failure medical therapy and hence expected by the nature of the disease and its treatment.

In addition patients will have additional blood draws to measures levels of natriuretic peptides. The risk associated with these blood draws are minimal and may include dizziness, fainting and other mild local reactions such as minimal bruising and hematoma. The amount of blood drawn will not exceed 20 cc throughout the study, which is regarded as insignificant from the perspective of generalized systemic effects.

2.3.2 KNOWN POTENTIAL BENEFITS

The potential benefit of participating in the study is that randomized patients will have a 50/50 chance of receiving standard of care tailored to their congestion, natriuretic peptide levels and hemodynamic status in an organized manner. Although tailored therapy to natriuretic peptide measurements has not been proved to improve patients' outcomes (Felker, Anstrom et al. 2017), we believe that a tailored approach to implementation of oral HF therapies early after an admission for acute heart failure may benefit those patients. In addition, patients randomized to the higher intensity arm will have access to the study team during the period of the study.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

In balance, patients randomized to the higher intensity arm will have access to a tailored implementation of oral HF therapies within the immediate period after an admission for acute heart failure. While some of the known side effects that can occur when administering these therapies may occur while these medications are administered and up titrated, these adverse effects have been deemed reasonable and the risk to benefit ratio of such therapies has been weighed and found to be acceptable by both regulatory authorities that approved those drugs for heart failure patients and the ESC guidelines recommending their use at the doses implemented in the study. Patients assigned to the "usual care" arm will be treated per standard local practice and will thus incur no increased risk other than that associated with additional blood draws.

3 OBJECTIVES AND ENDPOINTS

STRONG-HF is a multicenter, randomized, parallel group study is designed to evaluate the efficacy and safety of up-titration of standard of care medical therapy including beta-blockers, ACEi (or ARB if intolerant to ACEi) or ARNi and MRAs, on morbidity and mortality when initiated early during hospitalization for acute heart failure (AHF). Optimal safety conditions will allow physicians to introduce and/or continue oral HF therapies during the "vulnerable phase" in acute heart failure (AHF) patients.

The study's primary objective is to assess the effects of optimization of medical therapy with beta-blockers, ACEi (or ARB if intolerant to ACEi) or ARNi and MRAs on 180-day all-cause mortality or heart failure readmission in patients admitted with acute heart failure and clinical and biological signs of congestion. To address this objective, the primary endpoint is the occurrence of all-cause mortality or HF-readmission through 180 days post-randomization.

Secondary study objectives are to assess the effect of such intervention on change in quality of life (QoL) as measured by the EQ-5D questionnaire, 180-day all-cause mortality, and 90-day all-cause mortality or heart failure admission. Secondary endpoints addressing these objectives are

1. Change in quality of life measured by the EQ-5D questionnaire from randomization to day 90
2. 180-day all-cause mortality
3.
4. 90-day all-cause mortality or heart failure readmission

Cardiovascular mortality as well as HF readmissions are well-established and well-accepted measures of therapeutic benefit in HF (Zannad, Garcia et al. 2013). Patients discharged from an AHF admission are at increased risk of dying, particularly within the first 3 months following discharge (Chioncel, Mebazaa et al. 2017). They are also at risk of re-admission for worsening HF, which is important because patients who are readmitted very early add substantial burden to the health care system, and once readmitted are at further increased risk of death.

Heart failure is a leading cause of mortality and morbidity in the industrialized world; it limits quality of life and imposes a major societal burden. 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 standardized instrument developed by the EuroQoL Group (*www.euroqol.org*), and consists of a descriptive system of five dimensions – mobility, self-care, usual activities, pain/discomfort, and anxiety/depression – and a visual analog scale (VAS) on which the patient rates his or her health. The questionnaire is two pages long, which should take only a few minutes to complete (Oppe, Rabin et al. 2008), and can be self-completed or completed through face-to-face or telephone interview. Published studies support the validity and reliability of the EQ-5D as an outcome measure in cardiovascular disease (Dyer, Goldsmith et al. 2010).

Other endpoints include changes in biomarkers. While biomarker changes are not universally accepted as surrogates of clinical outcomes, they are indicators of safety and favorable changes may be associated with better longer-term outcomes (Zannad, Garcia et al. 2013).

Changes in the primary and secondary endpoints will be examined in pre-determined subgroups including Left Ventricular Ejection Fraction ≤ or > 40%. Pharmacoeconomic analyses, taking into account such cost drivers as urgent outpatient clinic or emergency department visits may also be performed.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This multicenter, randomized, parallel group study is designed to evaluate the efficacy and safety of up-titration of standard of care medical therapy including beta-blockers, ACEi (or ARB if intolerant to ACEi) or ARNi and MRAs, on morbidity and mortality when initiated and up-titrated early during hospitalization for acute heart failure (AHF). Optimal safety conditions will allow physicians to introduce and/or continue oral HF therapies during the "vulnerable phase" in acute heart failure (AHF) patients. Eighteen hundred (1800) patients in up to 90 centers admitted for AHF with clinical signs of congestion and elevated circulating NT-proBNP and who are not treated with optimal doses of oral HF therapies within 2 days before hospital discharge for AHF and who are hemodynamically stable will be randomized to usual care (named "usual care" arm) or intensification of treatment with beta-blockers, and ACEi (or ARB) or ARNi and a MRA (named "high intensity care" arm). Eligibility is based in part on screening levels of NT-proBNP and on changes in NT-proBNP from screening to pre-discharge; eligibility criteria are described in ***Section 5, Study Population*****.** Randomization will be stratified by country and mid-range/preserved (HFmrEF/HFpEF) versus reduced (HFrEF) ejection fraction. AHF patients who were screened but did not meet inclusion criteria, including low circulating NT-proBNP at visit 2, will also be followed for 90-day outcome (death and readmissions). Randomized patients will be contacted (by telephone) at 180 days after randomization.

Patients randomized to the "high intensity care" arm will follow an algorithm combining optimization of oral HF therapies and frequent visits, including circulating NT-proBNP measures, to assess congestion. The first dose adjustment occurs just following randomization at the Randomization visit (Visit 2, within 2 days before discharge), when patients will be prescribed medical therapy with beta-blockers, ACEi (or ARB if intolerant to ACEi) or ARNi and MRA adjusted to at least half the optimal doses.

These patients will be assessed by the study team at 1, 2, 3, and 6 weeks (Visits 3, 4, 5 and 6) following randomization. Safety and tolerability will be assessed at visits 3 to 6 by full physical examination, and laboratory assessments of NT-proBNP, sodium, potassium, glucose, and kidney function and hemoglobin measures. Safety and tolerability will be assessed at Visit 3 (1 week follow-up). At visit 4 (2 weeks following randomization) up-titration to full optimal doses of beta-blockers, ACEi/ARB/ARNi, and a MRA should be performed given adequate safety. Clinical assessments and follow-up measures of NT-proBNP will guide the safety of up-titrations of oral HF medications. Investigators will assess congestion, and increase diuretics as needed, based on those assessments. ACEi/ARB/ARNi and or MRAs will not be up-titrated if the systolic blood pressure is < 95 mmHg, serum potassium > 5.0 mmol/L or eGFR is < 30 ml/min/1.73m^2. Beta-blockers will not be up-titrated if heart rate < 55 bpm or systolic BP is < 95 mmHg. If the NT-proBNP level is >10% higher than the pre-discharge level, physicians should consider not up-titrating beta-blockers and consider increasing diuretics. Safety and tolerability will be assessed again at Visit 5 (3 weeks follow-up) and visit 6 (6 weeks follow-up). Additional visits will be done at 1 week following any up-titration to assess safety and tolerability.

All randomized patients, and screen failures, will be followed at 90 days for the occurrence of hospital re-admissions or death. Adverse events and outpatient visits will be collected through 90 days for all randomized patients. Events will be reported as they occur throughout the follow-up period. Randomized patients will be contacted at 180 days from randomization (90 days following completion of the treatment period) for a safety assessment of vital status and occurrence of rehospitalizations, and current prescriptions of oral HF medications.

An interim futility analysis was planned when 450 patients had 90-day follow-up available. An additional futility analysis is planned when approximately 1300 patients have 180-day follow-up available. It is not intended to stop the trial early on the basis of superior efficacy. If the estimated conditional power (CP) for the primary endpoint, assuming that the treatment effect assumed for the sample size in the protocol applies to the remainder of the study is <0.25, the DSMB may recommend that the study be discontinued for futility. No adjustment to the final alpha level is required for this futility analysis.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

In contrast to the lack of benefits of intravenous therapies in AHF, several classes of oral heart failure medications, including beta-blockers, ACEi, ARNi and MRA, have shown benefit on long-term outcome in chronic stable heart failure patients. No randomized controlled trial (RCT) has shown benefits of any specific therapy on either morbidity or mortality in acute heart failure. RCTs have mostly tested intravenous short-acting therapies (vasodilators or inotropes) in the initial phase after admission for acute heart failure and examined long-term outcome. Recently, it was suggested that oral heart failure therapies, especially the combination of beta-blockers and ACEi are associated with a rapid benefit on survival when given at discharge from AHF (Gayat, Arrigo et al. 2017). However, a large part of AHF patients are not adequately followed and undertreated during the “vulnerable phase” - the few months following discharge from AHF. This is associated with marked excess of hospital readmission and of death. Guidelines of Joint American Heart Association and American College of Cardiology (published in 2013, updated in 2017)(Yancy, Jessup et al. 2013; Yancy, Jessup et al. 2017) and HFSA (published in 2016)(Yancy, Jessup et al. 2016) give no indication on the number of visits after hospital discharge from an AHF episode. European Society of Cardiology (2016)(Ponikowski, Voors et al. 2016) recommends “a follow-up plan after discharge” and that “patients should preferably be seen by GP within a week of discharge, if feasible”; no indications were given for later visit(s). The other major issue is that guidelines do not indicate what to do during the post-discharge visit, though, no excess morbidity or mortality was shown by rapid optimization of oral HF therapies, physicians are afraid to optimize therapies after an episode of AHF.

In summary, clear and practical indications on ways to optimize “safely” oral heart failure medications during the “vulnerable” phase needs to be assessed. We propose combining optimization of oral HF therapies and frequent visits to assess persistent improvement in congestion. Thus, the “high intensity care” arm of STRONG-HF is designed to provide the best conditions for physicians to optimize oral HF therapies, including the use of ARNi, within 4 weeks after hospital discharge. To do so, STRONG-HF will select, during the index hospitalization and based on high circulating NT-proBNP, AHF patients with need of oral HF therapies. Circulating NT-proBNP will be further measured, repeatedly, during the post-discharge “vulnerable” phase to assess the optimization of oral HF therapies and specifically the continuous improvement of congestion. Patients randomized to the control group will continue to receive care as usual as per routine practice in their country and area of residence.

4.3 JUSTIFICATION FOR DOSE

Patients assigned to the “high intensity care” arm will be treated with oral medications for heart failure at the doses recommended in the prescribing information (package inserts) supplied by the manufacturers and as recommended in ESC guidelines for the treatment of patients with HFrEF (LVEF <40%). The target maintenance dose of the beta-blocker nebivolol will be the dose found to be effective in reducing the risk of death or CV admission in the SENIORS study (Flather, Shibata et al. 2005), as recommended in the ESC guideline. Although ESC guidelines do not specifically recommend the use of RAAS inhibitors or beta-blockers in patients with mid-range or preserved EF, nebivolol, spironolactone

and candesartan are recognized as having evidence that the risk of HF hospitalization is reduced with their use in patients with HFpEF. A recent meta-analysis of randomized clinical trials suggests an approximate 10% reduction in the risk of HF hospitalization associated with the use of ACEi or ARB in patients with HFpEF (hazard ratio 0.91, 95% CI 0.83-1.01) (Khan, Fonarow et al. 2017).

4.4 END OF STUDY DEFINITION

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

The end of the study is defined as completion of the last visit 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. Hospital admission within the 72 hours prior to Screening for acute heart failure with dyspnea at rest and pulmonary congestion on chest X-ray, and other signs and/or symptoms of heart failure such as edema and/or positive rales on auscultation.
2. All measures within 24 hours prior to Randomization of systolic blood pressure ≥ 100 mmHg, and of heart rate ≥ 60 bpm.
3. All measures within 24 hours prior to Randomization of serum potassium ≤ 5.0 mEq/L (mmol/L).
4. Biomarker criteria for persistent congestion:
    a. At Screening, NT-proBNP > 2,500 pg/mL.
    b. At the time of Randomization (within 2 days prior to discharge), NT-proBNP > 1,500 pg/mL (to ensure the persistence of congestion) that has decreased by more than 10% compared to Screening (to ensure the acuity of the index episode).
5. At 1 week prior to admission, at Screening, and at Visit 2 (just prior to Randomization) either (a) ≤ ½ the optimal dose of ACEi/ARB/ARNi (see ***Table***) prescribed, no beta-blocker prescribed, and ≤ ½ the optimal dose of MRA prescribed or (b) no ACEi/ARB/ARNi prescribed, ≤ ½ the optimal dose of beta-blocker prescribed, and ≤ ½ the optimal dose of MRA prescribed.
6. Written informed consent to participate in the study.

5.2 EXCLUSION CRITERIA

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

1. Age < 18 or > 85 years.
2. Clearly documented intolerance to high doses of beta-blockers.
3. Clearly documented intolerance to high doses of RAS blockers (both ACEi and ARB).
4. Mechanical ventilation (not including CPAP/BIPAP) in the 24 hours prior to Screening.
5. Significant pulmonary disease contributing substantially to the patients' dyspnea such as FEV1< 1 liter or need for chronic systemic or nonsystemic steroid therapy, or any kind of primary right heart failure such as primary pulmonary hypertension or recurrent pulmonary embolism.

6. 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 Screening.
7. 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 exclusion.
8. Uncorrected thyroid disease, active myocarditis, or known amyloid or hypertrophic obstructive cardiomyopathy.
9. History of heart transplant or on a transplant list, or using or planned to be implanted with a ventricular assist device.
10. Sustained ventricular arrhythmia with syncopal episodes within the 3 months prior to screening that is untreated.
11. 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.
12. Active infection at any time during the AHF hospitalization prior to Randomization based on abnormal temperature and elevated WBC or need for intravenous antibiotics.
13. Stroke or TIA within the 3 months prior to Screening.
14. Primary liver disease considered to be life threatening.
15. Renal disease or eGFR < 30 mL/min/1.73m^2 (as estimated by the simplified MDRD formula) at Screening or history of dialysis.
16. Psychiatric or neurological disorder, cirrhosis, or active malignancy leading to a life expectancy < 6 months.
17. Prior (defined as less than 30 days from screening) or current enrollment in a CHF trial or participation in an investigational drug or device study within the 30 days prior to screening
18. Discharge for the AHF hospitalization anticipated to be > 14 days from admission, or to a long-term care facility. Randomization must occur within 12 days following admission and at within 2 days prior to anticipated discharge.
19. Inability to comply with all study requirements, due to major co-morbidities, social or financial issues, or a history of noncompliance with medical regimens, that might compromise the patient's ability to understand and/or comply with the protocol instructions or follow-up procedures
20. Pregnant or nursing (lactating) women.

5.3 LIFESTYLE CONSIDERATIONS

All patients will be provided with information regarding lifestyle advice according to ESC and local guidelines, although there is little evidence that they improve prognosis.

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. 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 to be reported in the CRF includes demography, screen failure details and eligibility criteria.

Patients who were screened but did not meet inclusion criteria, including low circulating NT-proBNP at visit 2, will be followed for 90-day outcome (death and readmissions).

Individuals who do not meet the criteria for participation in this trial (screen failure) may not be rescreened.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 INITIAL SCREENING AND DOSING

To qualify for randomization, patients must meet biomarker criteria evidencing persistent congestion. At Screening, qualifying patients must have NT-proBNP greater than 2,500 pg/mL. At the time of randomization (within 2 days prior to discharge), NT-proBNP must be greater than 1,500 pg/mL (to ensure the persistence of congestion) and must have decreased by more than 10% compared to baseline (to ensure the acuity of the index episode).

At 1 week prior to admission, at Screening, and at Visit 2 either ≤ ½ the optimal dose of ACEi/ARB/ARNi (see ***Table***) and no beta-blocker must have been prescribed or ≤ ½ the optimal dose of beta-blocker and no ACEi/ARB/ARNi must have been prescribed, and ≤ ½ the optimal dose of MRA must have been prescribed. Eligible patients meeting these and all other eligibility criteria will be randomized to the "high intensity care" arm (***Section 6.1.2***) or the "usual care" arm (***Section 6.1.3***) in a 1:1 ratio.

Table. Optimal doses of heart failure oral medications

Medication generic name	Dose (half daily dose) at Visit 2	Optimal (full) dose at Visit 4
MRA		
Eplerenone	25 mg q.d.	50 mg q.d.
Spironolactone	25 mg q.d.	50 mg q.d.
Beta-blocker		
Bisoprolol	5 mg q.d.	10 mg q.d.
Carvedilol	12.5 – 25 mg b.i.d.	25 – 50 mg b.i.d.
Metoprolol succinate extended-release tablet	100 mg q.d.	200 mg q.d.
Nebivolol	5 mg q.d.	10 mg q.d.
ACEi		
Captopril	25 mg t.i.d.	50 mg t.i.d.
Enalapril	10 mg b.i.d.	20 mg b.i.d.
Lisinopril	17.5 mg q.d.	35 mg q.d
Ramipril	2.5 mg b.i.d. or 5 mg q.d.	5 mg b.i.d. or 10 mg q.d.

Medication generic name	Dose (half daily dose) at Visit 2	Optimal (full) dose at Visit 4
Trandolapril	2 mg q.d.	4 mg q.d.
Perindopril	4 mg q.d.	8 mg q.d.
ARB		
Candesartan	16 mg q.d.	32 mg q.d..
Valsartan	80 mg b.i.d.	160 mg b.i.d.
Losartan	75 mg q.d.	150 mg q.d.
ARNi		
Sacubitril/valsartan (Entresto™)	49/51 mg b.i.d.	97/103 b.i.d.

6.1.2 "HIGH INTENSITY CARE" ARM

The "high intensity care" arm will follow an algorithm combining immediate optimization of oral HF therapies and frequent visits, including measurement of circulating NT-proBNP measures, to assess congestion.

Just following randomization at Visit 2 (within 2 days prior to discharge), patients randomized to the "high intensity care" arm will be prescribed medical therapy with beta-blockers, ACEi (or ARB if intolerant to ACEi) or ARNi and MRA adjusted to at least half the optimal doses. Optimal doses of HF medications are given in the ***Table*****.** In patients hemodynamically stable, it will be recommended to achieve the target therapy dose (half the maximal recommended dose) in the same day (for all 3 classes of HF therapies). If needed, beta-blockers and MRA can be given in one day (the day before discharge) and ACEi (or ARB or ARNi) the following day (the day of discharge).

These patients will then be assessed by the study team at 1,2, 3, and 6 weeks (Visits 3, 4, 5 and 6) following randomization. Safety and tolerability will be assessed at visits 3 to 6 by full physical examination, and laboratory assessments of NT-proBNP, sodium, potassium, glucose, and kidney function and hemoglobin measures. At visit 4 (2 weeks following randomization), up-titration to full optimal doses of beta-blockers, ACEi/ARB/ARNi, and a MRA should be performed given adequate safety. Clinical assessments and follow-up measures of NT-proBNP will guide the safety of up-titrations of oral HF medications. If at a certain visit up-titration is not possible, further attempts to up-titrate should be made in following visits. Investigators will assess congestion, and increase diuretics as needed. ACEi/ARB/ARNi and or MRAs will not be up-titrated if the systolic blood pressure is < 95 mmHg, serum potassium > 5.0 mmol/L or eGFR is < 30 ml/min/1.73m^2. If eGFR alone is < 30 ml/min/1.73m^2 investigators are encouraged to reduce the dose of diuretics, if those are deemed high or have been recently up-titrated. Beta-blockers will not be up-titrated if heart rate < 55 bpm or systolic BP is < 95 mmHg. If the NT-proBNP level is >10% higher than the pre-discharge level physicians should consider not up-titrating beta-blockers and consider increasing diuretics. Safety and tolerability will be assessed again at Visit 5 (3 weeks follow-up) and visit 6 (6 weeks follow-up).
Where sodium-glucose cotransporter (SGLT) inhibitors are available, investigators are encouraged to prescribe them as early as possible to patients during the hospitalization phase. In addition, before discharge, investigators are encouraged to treat patients who have low levels of ferritin (<100 µg/L) with intravenous ferric carboxymaltose.

At each visit, if the patient is not on maximally tolerated doses of beta-blockers and/or ACEi/ARBs/ARNi and based on the above criteria it is deemed safe to up-titrate these medications, the medications should be up-titrated.

Additional visits will be done at 1 week following any up-titration to assess safety and tolerability at which time full physical examination, and laboratory assessments of NT-proBNP, serum sodium, serum potassium and kidney function measures will be performed.

6.1.3 "USUAL CARE" ARM

In the "usual care" arm, patients will be followed by the patient's cardiologist and/or general physician as per usual care practiced in the country and their community. The patient's next contact with the investigator will be at the 90- day visit.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Not applicable, because no study medication is provided for this study.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Not applicable, because no study medication is provided for this study.

6.2.3 PRODUCT STORAGE AND STABILITY

Not applicable, because no study medication is provided for this study.

6.2.4 PREPARATION

Not applicable, because no study medication is provided for this study.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Patients meeting eligibility criteria will be randomized to one of the two study arms in a 1:1 ratio, according to a central randomization scheme stratified by HFmrEF/HFpEF versus HFrEF, and country. No investigator will have access to the randomization scheme during the course of the study. The investigator or the investigator's delegate will log in to the IWRS part of the electronic data system, and be notified of the patient's assigned study arm.

Patients who are randomized in error, i.e., patients who did not meet eligibility requirements for whom the IWRS was contacted and a randomization conducted in error, should be considered screen failures and handled as described in ***Section 5, Screen Failures***. The Investigator will notify the Data Coordinating Center immediately of any randomization errors. Patients randomized in error will not be replaced, but enrollment will continue until 1800 patients are correctly randomized.

This is an open-label study, where treatment assignments are known to the investigator. To prevent crossover with respect to study therapy adjustment strategies, patients randomized to the "usual care" arm will be discharged to care by their general physician and/or their cardiologist, according to standard local practice. The follow-up schedule and HF medication management will be left to the treating physician's discretion.

6.4 STUDY INTERVENTION COMPLIANCE

For patients enrolled in the "high intensity care" arm, the prescribed doses of HF medications – including ACEi, ARB, and/or ARNi; beta-blocker; MRA; and diuretics – will be recorded at every visit. Data affecting the dosing algorithm, including biomarker values and HF signs and symptoms, will be recorded promptly in the CRF following each patient visit. The investigator's compliance with the dosing adjustment algorithm will be monitored centrally.

For patients enrolled in the "usual care" arm, prescribed doses of HF medications will be recorded at Visits 1 (Screening), 2 (within 2 days prior to discharge), and 7 (90 days-follow-up).

6.5 HEART FAILURE MEDICATIONS AND CONCOMITANT THERAPY

No medication use specifically renders a patient ineligible to participate in the study, with the exception of treatment with an investigational drug or device within 30 days prior to Screening. Patients with a known history of noncompliance to medical regimes are ineligible for the study. Patients treated with cardiac surgery or who have had a CRT device implantation with the 3 months or including PTCI within 1 month prior to Screening, or who have received a heart transplant or are on a transplant list, or are using or planned to be using an implanted ventricular assist device are ineligible for the study.

Major cardiovascular (including HF medications) and non-cardiovascular classes of medication prescribed to be taken by a subject will be recorded at each study visit. These medications include but are not limited to loop diuretics, other diuretics, ACE inhibitors, angiotensin receptor antagonists, MRA, beta-blocker, hydralazine, nitrates, calcium channel blockers, digoxin, ivabradine, non-steroidal anti-inflammatory agents, COX-2 inhibitors, aminoglycoside antibiotics, inotropes, vasodilators and others (e.g. insulin, oral antidiabetics, statins, anticoagulants). Any medical procedures and significant non-drug therapies administered after the patient was randomized in the study should be recorded at each study visit in the patient's medical record.

During the study, the investigator may prescribe any additional medications to patients enrolled in the "high intensity care" arm as dictated by the patients' condition. Administration of standard treatment should in no instance be delayed or withheld due to the patient's participation in the study.

6.5.1 RESCUE MEDICINE

The investigator may prescribe any medications and/or supportive care during the study based on clinical needs, as per European and local guidelines. Other cardiovascular medications (such as ivabradine) can be prescribed if indicated as per ESC guidelines. The use of concomitant medications or medical procedures should be recorded in the appropriate section of the CRF.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Patients can refuse to participate in specific aspects of the study and/or take prescribed medication(s) at any time without fully withdrawing consent (see ***Section 7.2, Participant Discontinuation/Withdrawal from the Study***) and permission should be requested of the patient to conduct follow-up visits or calls. The Investigator should make every effort to accommodate the needs of the patient to make it possible for them to continue to participate in the remaining aspects of the study. This includes performing

telephone visits to obtain health status and/or mortality information for patients who are unable to or refuse to return for clinic visits.

Discontinuation from specific aspects of the study (including refusal to comply with prescribed medication doses) does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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.

Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for a scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within the week of contact, if possible, and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file, and should continue until just prior to database lock.
- Should every effort to contact the patient be exhausted and the investigator is unable to contact the participant at the time of database lock, the patient will be considered to have discontinued from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

8.1.1 Assessment of clinical endpoints

All events of death and rehospitalizations from Randomization (or from determination of screen failure status for Screen Failure patients) through visit 7 (90-day follow-up) will be recorded. Deaths and rehospitalizations occurring between visit 7 (90-day follow-up) and visit 8 (180-day follow-up contact) will be additionally recorded for randomized patients. A rehospitalization is defined as an unplanned overnight stay in the hospital, regardless of whether the patient was admitted. Every effort (consistent with all applicable laws and regulations) will be made to obtain vital status on all randomized subjects, including those subjects who withdraw consent - see ***Section 7.2, Participant Discontinuation/Withdrawal from the Study*** – or who are lost to follow-up – see ***Section 7.3, Lost to Follow-up***.

8.1.2 Quality of life questionnaire administration

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.

Validated translations of the EQ-5D for self-completion are available in multiple languages. The questionnaire should be completed by the patient in a quiet, private space prior to any invasive or demanding study or routine procedures, e.g., blood draws. If the patient attends the visit but is unable to self-complete the questionnaire, it may be administered through face-to-face interview following the face-to-face interview script. The questionnaire should be administered to the patient in a language in which the patient is fluent, using an official validated translation, and the same language used for both baseline and follow-up assessments.

8.2 SAFETY AND OTHER ASSESSMENTS

8.2.1 Medical history and demographics

Detailed information regarding the patient's demographics and medical history will be obtained through review of the patient's medical record for relevant conditions present prior to Screening. Demographic information to be recorded includes the patient's age, sex at birth, race and ethnicity (where permitted to be recorded), and socioeconomic status indicators including but not necessarily limited to education level and household income.

8.2.2 Chest X-ray (radiography)

Eligible patients should have evidence of pulmonary congestion on chest x-ray at Screening. The X-ray is expected to have been taken during the admission process as part of routine standard of care, prior to obtaining informed consent, and is not a study-related procedure but part of the patient's medical history. The X-ray must have been interpreted by a qualified cardiologist (e.g., the investigator) or radiologist.

8.2.3 Electrocardiography (ECG)

The ECG is expected to have been obtained during the admission process as part of routine standard of care, prior to obtaining informed consent, and is not a study-related procedure but part of the patient's

medical history. Patients whose AHF was triggered primarily by significant arrhythmias or with evidence of myocardial infarction should not be enrolled in the trial. Patients with a history of atrial fibrillation/flutter or with atrial fibrillation/flutter present are eligible to participate.

8.2.4 Echocardiography

The last quantitative left ventricular ejection fraction (LVEF) measured using echocardiography or other method within the 6 months prior to screening, including during the index HF hospitalization, will be recorded. This assessment is expected to have been performed as standard of care for heart failure and is required for randomization, but is not considered a study-related procedure but as part of the patient's medical history. Randomization will be based upon this baseline LVEF measure where LVEF ≤ 40% will be considered HFrEF and > 40% will be considered HFmrEF/HFpEF.

8.2.5 Physical examination – clinical HF assessment

A complete physical examination will be performed at Visit 2 (within 2 days before discharge) and Visit 7 (90-day follow-up) in all randomized patients. Patients randomized to the "high intensity care" arm will have further assessments at each follow-up visit. Any relevant clinically significant abnormalities at Visit 2 should be recorded in the CRF as part of the medical history. Any relevant clinically significant changes noted at follow-up should be reported as an adverse event.

At baseline and during follow-up, the investigator will evaluate symptoms and signs of heart failure, with particular attention to evidence of congestion including dyspnea on exertion or at rest, orthopnea, rales, jugular venous pulse (JVP) and peripheral edema. To reduce variability and increase sensitivity to detect changes, these evaluations should be done at the same time of day, in the same position(s), and, preferably, in the same setting and by the same assessor.

8.2.6 Biological specimen collection and laboratory evaluations

8.2.6.1 Local laboratory measures

Blood samples (plasma or serum) will be taken at Visits 1 (Screening) and 2 (within 2 days prior to discharge) in screened patients; Visit 7 (90-day follow-up) in all randomized patients; and at Visits 3, 4, 5 and 6 in patients randomized to the "high intensity care" arm for routine hematology and clinical chemistry (including serum sodium, potassium, and kidney function measures) and for analysis of NT-proBNP by the local laboratory using commercially available assays.

8.2.6.2 Biobanking

Blood samples (serum and plasma) will be taken at Visits 2 (within 2 days prior to discharge) and 7 (90-day follow-up) in all randomized patients. Samples will be stored frozen locally until shipped for longer-term storage and analysis. Further details are provided in the Laboratory Procedures Manual.

8.2.7 Vital signs

Vital signs, including temperature, pulse, respirations, blood pressure, and body weight recorded as part of routine standard of care during the admission and prior to Screening are considered part of the medical history required to assess study eligibility. Vital signs measures at Visits 2 and 7 in all randomized patients, and at all follow-up visits in patients randomized to the "high intensity care" arm, will be made with the patient in a sitting position after resting for at least 5 minutes. Systolic and diastolic blood pressure should be measured 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. Height should be measured at Visit 1 (Screening) in all screened patients. Body weight should be measured at Visits 1 and 2 in screened patients, at visit 7 in all randomized patients, and at all follow-up visits in

patients randomized to the “high intensity care” arm. To reduce variability, the same scale should be used throughout if possible.

8.2.8 Assessment of adverse events

The patient should be asked at each study visit regarding the occurrence of any adverse events (AEs). Non-serious AEs with an onset from the time of signing the study Informed Consent through 90 days post-randomization will be recorded for randomized patients. Serious AEs will be recorded from signing informed consent through 90 days post-randomization for randomized patients.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- a congenital anomaly/birth defect, or
- an important medical event that may not result in death, be life-threatening, or require hospitalization when, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Only hospitalizations or prolongations of hospitalizations that are associated with an AE should be considered a SAE. The following hospitalizations, for example, would not constitute SAEs: a hospitalization or prolongation of a hospitalization that is part of a routine procedure followed by the study site (e.g., stent removal after surgery), a hospitalization for survey visits or annual physicals, a hospitalization planned before the start of the study for a preexisting condition that has not worsened.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **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

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 determining whether an adverse event (AE) is expected or unexpected. An AE 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 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 intervention (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.

The investigator or designee will record all reportable events with start dates occurring any time after informed consent is obtained through 90 days post-randomization for randomized subjects. 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.

8.3.5 ADVERSE EVENT REPORTING

The investigator will record the occurrence of adverse events in the CRF. Serious AEs should be reported within 24 hours of knowledge of the event. The Medical Monitor will be responsible for reviewing SAEs as they are reported, and will share information with the DSMB regarding SAE occurrence as described in the DSMB Charter.

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, 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 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 REPORTING EVENTS TO PARTICIPANTS

Not applicable.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.3.9 REPORTING OF PREGNANCY

As all medications administered to patients in the current study are administered within the approved indications and recommended guidelines, all pregnancies will be handled in accordance with the package inserts of the prescribed drugs, which will differ from patient to patient.

Any pregnancy that occurs following randomization through Visit 7 should be reported to the Data Coordinating Center and to the Sponsor.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary hypothesis is that the cumulative proportion of patients who died or were readmitted for HF readmission at 180 days post-randomization is less in the “high intensity care” group than in the “usual care” group.

The formal statistical null (H_0) and alternative (H_a) hypotheses are

H_0: $d \geq 0$

H_a: $d < 0$,

where d is the weighted average difference – in Cohort 1 and Cohort 2 – in Kaplan-Meier estimates of the cumulative proportion of patients with the primary endpoint at Day 180, adjusted for randomization stratification factors in the “high intensity care” and “usual care” groups.

The primary hypothesis will be tested in patients randomized for whom Day 180 follow-up is expected per protocol, and will exclude patients randomized in error. Results in the cohort in whom the first interim analysis of the Day 180 endpoint was conducted (“Cohort 1”) and in the cohort of patients (“Cohort 2”) randomized after 7 February 2020 will be included, with down-weighting of the Cohort 1 result by half its sample size. Sensitivity analyses will be conducted varying the weight of the Cohort 1 result.

9.2 SAMPLE SIZE DETERMINATION

The observed cumulative rate of CV death or readmission due to HF or renal failure through 90 days post-randomization was approximately 17% the placebo control arm of the RELAX-AHF-2 study. In the RELAX-AHF-2 study, patients with BNP ≥500 pg/mL or NT-proBNP ≥2000 pg/mL (or BNP ≥750 pg/mL or NT-proBNP ≥3000 pg/mL if in atrial fibrillation), eGFR ≥25 and ≤75 mL/min/1.73 m^2, and systolic BP ≥125 mmHg were randomized within 16 hours of presentation to the hospital for acute heart failure and

followed for 180 days. In the ASTRONAUT study, hemodynamically stable, hospitalized chronic heart failure patients with LVEF ≤ 40%, and BNP ≥ 400 pg/mL or NT-proBNP ≥ 1600 pg/mL were randomized prior to discharge a median of 5 days from hospital admission. In the EVEREST trial, the rate of CV death or HF hospitalization at 3 months was 20%. The observed rate of CV death or HF hospitalization through 90 days from randomization in the control arm (placebo plus standard care) of the ASTRONAUT study was approximately 18% (Gheorghiade, Bohm et al. 2013). In the EVEREST trial, patients with LVEF ≤ 40% and hospitalized for heart failure were randomized within 48 hours of admission. The reported rate of CV death or HF hospitalization at 3 months was 20% (Konstam, Gheorghiade et al. 2007). Analysis of combined studies (unpublished data) of patients recently discharged from an AHF admission, suggest that patients with high natriuretic peptide levels both near the time of admission and at discharge are at higher risk of this outcome. The vast majority of deaths observed in the control groups in these studies in this timeframe were due to cardiovascular causes, thus, a 90-day event rate of 20% in patients receiving usual care was initially assumed in this study. However, interim results suggest that the 90-day event rates in the STRONG-HF study are lower than anticipated, with a predicted rate in the control arm at 180 days closer to 20%.

With randomization of a total of 1800 patients, "Cohort 2" will include approximately 1370 patients. The treatment groups will be compared using a test, which is distributed as chi-square with 1 df, derived from the weighted average difference across Cohorts 1 and 2 of the adjusted Kaplan-Meier estimates of the proportions with the primary endpoint at Day 180 in each group and their associated standard errors.

Power was computed as the proportion of 10,000 simulated trials where $p<0.05$ for the chi-square statistic. For each simulated trial, the weighted average difference in event rates was computed from the preliminary observed result in Cohort 1 and assumed binomial distributions for the given active and control rates for the additional 685 Cohort 2 patients per group randomized 1:1. Assuming that 20% of patients in the "usual care" group die or are re-admitted for HF within 180 days, 685 additional patients per treatment group (for a total enrollment of 1800 patients) provides approximately 89% power for the chi-square test to detect a difference of 6% (14% versus 20%), and approximately 75% power to detect a difference of 5% (15% versus 20%), at the two-sided 0.05 significance level.

Because the planned futility analyses *(*see ***Section 9.4.6, Planned Interim Analyses****)* will not affect the study's false-positive rate, the final alpha level will not be adjusted.

9.3 POPULATIONS FOR ANALYSES

The following population will be used for the statistical analyses:

- **Full Analysis set (FAS)**. The FAS will consist of all randomized patients with the exception of those patients who were randomized in error (see ***Section 6.3, Measures to Minimize Bias: Randomization and Blinding***). Following the intent-to-treat principle, patients will be analyzed according to the treatment to which they were assigned at randomization. Efficacy variables will be analyzed based on the FAS as the primary analysis population.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Unless otherwise specified, all hypothesis tests will be reported as 2-sided. Missing data will not be imputed in the primary analysis of secondary and exploratory outcomes. Subject disposition, demographics, baseline characteristics, and medication use will be summarized.

Continuous variables will be summarized using descriptive statistics, including the number of non-missing observations (n), mean, standard deviation, median, the first and third quartiles, minimum, and maximum. Highly skewed continuous variables may be log-transformed for analysis, in which case, the geometric mean and 95% confidence interval will be presented instead of the mean and standard deviation. Categorical variables will be summarized using the absolute and relative frequency of responses among those patients with a non-missing response for the given variable.

Details regarding the statistical analyses will be described in the Statistical Analysis Plan (SAP).

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint constitutes 180-day all-cause mortality or HF readmission. The difference in 180-day event rates between study arms will be computed from Kaplan-Meier estimates adjusted for randomization strata using Mantel-Haenszel weights. The test statistic, which is distributed as chi-square with 1 df, will be computed d^2/v, where d is the difference in event rates in the two groups and $v= SE_{HIC}^2 + SE_{UC}^2$. SE_{HIC} and SE_{UC} are the associated standard errors in the high intensity care and usual care groups, respectively. Kaplan-Meier estimates will be computed from the time from randomization to the first HF rehospitalization or death calculated in days through day 180. Patients without a prior event who withdraw consent or who are lost to follow-up without an event will be censored at the earlier of 180 days or the last date the patient was known to be alive. The two treatment groups will be compared at the two-sided 5% significance level (equivalent to a one-sided 2.5% significance level).

The primary hypothesis will be tested in the FAS where Day 180 follow-up is expected, with down-weighting of the result in Cohort 1 (patients enrolled prior to 8 February 2020, in whom the first interim analysis of the Day 180 endpoint was conducted), with f=0.5 in the following formula. Sensitivity analyses will include with various weights the result in Cohort 1 – including disregarding the Cohort 1 result (f=0) and giving Cohort 1 full weight according to its sample size (f=1). The weighted average difference, d, in proportions will be calculated as

$$d = w*d_1 + (1-w)*d_2$$

$$\text{with variance } v = (w^2)*v_1 + (1-w)^2*v_2$$

where

- d_1 and d_2 are the group differences in proportions for Cohort 1 and Cohort 2, respectively,
- $w = (f*N_1)/(f*N_1+N_2)$,
- N_1 and N_2 are the total numbers of patients in Cohort 1 and Cohort 2, respectively,
- f is a down-weighting factor between 0 and 1, such that f=1 implies no down-weighting and f=0 implies disregarding the initial data,
- v_1 and v_2 are the variances derived as the sum of the squared Kaplan-Meier associated standard errors in the two treatment groups, in Cohort 1 and Cohort 2, respectively.

The test statistic, computed as d^2/v, is distributed as chi-square with 1 df.

The primary analysis is equivalent to setting f=0.5. Sensitivity analyses will be conducted using f=1 (fully weighting the Cohort 1 result according to its sample size) and f=0 (disregarding the result in Cohort 1). The result for Cohort 1 will be based on final data.

The primary analyses will be conducted in the FAS.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINTS

The Type I error will be controlled across the secondary endpoints at the two-sided 0.05 significance level through a step-down approach. If the result for the primary efficacy endpoint is statistically significant, testing will proceed to the first secondary endpoint. If that result is statistically significant at two-sided $p<0.05$, testing will proceed to the second secondary endpoint, and so on.

9.4.3.1 Change in quality of life

The first secondary endpoint will be the change from Visit 2 (baseline) to Visit 7 (day 90) in the EQ-5D visual analog scale (VAS) score. Treatment groups will be compared with respect to observed values using ANCOVA with baseline EQ-VAS and randomization stratification factors as covariates. Additional analyses exploring the effect of missing values will be described in the SAP.

Supportive analyses will include presentation of the cross-classification of the Pre-discharge by follow-up responses for each of the 5 health dimensions for each treatment (shift table) at Visits 2 and 7. Treatment groups will be compared with respect to the ordered responses for each of the five health dimensions separately at Visit 7 using a stratified Mann-Whitney estimator with the baseline value as a covariable and stratified by randomization strata (Kawaguchi & Koch, 2015). The results will presented as the Mann-Whitney odds with the associated confidence interval and p-value.

An EQ-5D index will also be computed from the health states (unique combinations of responses to the 5 questions) by applying weights according to the Europe value set at each time point (Szende, Janssen et al. 2014). Treatment groups will be compared with respect to the change in the EQ-5D index using ANCOVA with the Visit 2 (baseline) value as a covariate.

9.4.3.2 Clinical outcomes

The second and third secondary endpoints constituting clinical outcomes include:

- 180-day all-cause mortality, and
- 90-day all-cause mortality or HF readmission.

The difference between treatment groups in the cumulative proportion of patients with respect to each of these events will be estimated and tested using methodology as described for the analysis of the primary endpoint. These proportions and their associated standard errors will be computed from Kaplan-Meier estimates adjusted for randomization strata using Mantel-Haenszel weights. The primary analysis of the 180-day risk differences will be analyzed in the FAS where Day 180 follow-up is expected, and down-weighting the Cohort 1 result (f=0.5). The primary analysis of 90-day risk differences will

include all patients in the FAS from Cohorts 1 and 2, i.e., using f=1 in the formulae in section ***9.4.2 Analysis of the Primary Efficacy Endpoint***.

For the composite endpoint of 90-day all-cause mortality or HF readmission, the time from randomization to the first occurrence of heart failure readmission or death will be calculated in days through day 90.

For either outcome, patients without a prior event who withdraw consent or who are lost to follow-up without an event will be censored at the earlier of the end of the period of interest (i.e., 90 or 180 days) or the last date the patient was known to be alive.

9.4.4 SAFETY ANALYSES

9.4.4.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of adverse events with an onset after randomization through 90 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 in the FAS. Treatment-related adverse events are those that are considered by the investigator as possibly, probably, or definitely related to the study intervention.

9.4.4.2 Vital Signs

Vital signs (Blood pressure, heart rate, temperature, and respiratory rate) and their changes from baseline will be summarized at each scheduled visit by treatment group. A comparison between groups for the change from baseline to visit 7 will be analyzed using an ANCOVA model with terms for treatment arm and adjusted by the baseline value and randomization strata.

9.4.4.3 Laboratory Evaluations

Local laboratory values and their changes from baseline will be summarized at each scheduled visit by treatment group. A comparison between groups for the change from baseline to visit 7 will be analyzed using an ANCOVA model with terms for treatment arm and adjusted by the baseline value and randomization strata.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Patient demographics, medical history, and baseline characteristics including the randomization stratification factors will be summarized by treatment group in the FAS. Proportions of patients meeting all eligibility criteria will be given. For descriptive purposes, treatment groups will be compared with respect to categorical variables using chi-square tests, and with respect to continuous variables using two-sample t-tests.

9.4.6 PLANNED INTERIM ANALYSES

An interim futility analysis was planned when 450 patients had 90-day follow-up available. An additional interim analysis is planned when approximately 1300 patients have been enrolled (combined Cohorts 1 and 2) and have 180-day follow-up available. If the estimated conditional power (CP) for the primary

endpoint, assuming that the treatment effect assumed for the sample size in the protocol applies to the remainder of the study is <0.25, the DSMB may recommend that the study be discontinued for futility. No adjustment to the final alpha level is required for these futility analyses.

9.4.7 SUB-GROUP ANALYSES

The effect of the intervention on the primary efficacy endpoint – 180-day all-cause death or HF rehospitalization – will be assessed over the following subgroups in Cohort 2 of the FAS where Day 180 follow-up is expected:

Age: ≤ 65 v. > 65 years, ≤ 75 v. > 75 years
Baseline LVEF: ≤ 40% v. > 40%
Baseline SBP: ≤ median v. > median
Baseline NT-proBNP: ≤ median v. > median
Atrial fibrillation/flutter at baseline: yes v. no

For each factor, the subgroup-by-treatment group interaction will be assessed using a test statistic constructed from the unadjusted estimates of the treatment difference in event rates and associated standard errors in each level of the subgrouping factor:

$$(d_{S1} - d_{S2})^2/(v_{S1} + v_{S2})^2$$

where

- d_{S1} and d_{S2} are the treatment group differences in proportions for subgroups 1 and 2 of the factor, respectively, and
- v_{S1} and v_{S2} are the variances derived as the sum of squared Kaplan-Meier associated standard errors in the two treatment groups in subgroups 1 and 2 of the factor, respectively.

The test statistic is distributed as chi-square with 1 df.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual patient data will not be listed.

9.4.9 EXPLORATORY AND SUPPORTIVE ANALYSES

9.4.9.1 Clinical Outcomes

Secondary endpoints constituting clinical outcomes include the following:

- 180-day all-cause mortality,
- 180-day CV mortality,
- 90-day all-cause mortality or heart failure readmission,
- 90-day HF readmission, and
- 180-day HF readmission.

The difference between treatment groups in the cumulative proportion of patients with respect to each of these events will be estimated and tested using methodology as described for the analysis of the

primary endpoint. These proportions and their associated standard errors will be computed from Kaplan-Meier estimates adjusted for randomization strata using Mantel-Haenszel weights. The primary analysis of the 180-day risk differences will be analyzed in the FAS where Day 180 follow-up is expected, and down-weighting the Cohort 1 result (f=0.5). The primary analysis of 90-day risk differences will include all patients in the FAS from Cohorts 1 and 2, i.e., using f=1 in the formulae in section ***9.4.2 Analysis of the Primary Efficacy Endpoint***.

For the composite endpoint of 90-day all-cause mortality or HF readmission, the time from randomization to the first occurrence of heart failure readmission or death will be calculated in days through day 90. The time to the first HF admission will be included in the analyses of 90-day and 180-day HF readmission, with the follow-up time censored at the time of death in those patients who die without a prior HF readmission within the period of consideration. For all these endpoints, patients without a prior event who withdraw consent or who are lost to follow-up without an event will be censored at the earlier of the end of the period of interest (90 or 180 days) or the last date the patient was known to be alive.

9.4.9.2 Hierarchical Composite Endpoint

Treatment groups will be compared with respect to a hierarchy of outcomes comprising all-cause death through day 90, HF hospitalization through day 90, and change in EQ-VAS from baseline to Visit 7 (Day 90) using the Finkelstein-Schoenfeld method (1999). In this extension of the Wilcoxon-Mann-Whitney rank sum test, each patient is compared with every other patient with respect to a hierarchy of outcomes, starting at the top of the hierarchy. At each step, if the pair is tied the comparison moves to the next step in the hierarchy until all levels are exhausted. Pairs tied at the last level remain tied. Groups are compared using a test statistic constructed from the individual pairwise comparisons.

Component	Pairwise comparison
Death through day 90	• If one patient died and other did not, then the one who died did worse; • If neither died, compare on next component.
Number of HF rehospitalizations through day 90	• Compare patients with respect to the number of HF rehospitalizations. The patient with more HF hospitalizations did worse. • If the two patients had the same number of HF hospitalizations, compare on next component.

Change in EQ-VAS from baseline to Day 90 visit	• Compare patients with respect to EQ-VAS change in 7 categories: >= 8 points worse 4-8 points worse 4 points worse to <0 no change (change of 0) >0 to 4 points better 4-8 points better >= 8 points better The patient with the lower category did worse. • If both patients in the same category, the pair remains tied.

9.4.9.3 Change in NT-proBNP levels

Treatment groups will be compared with respect to the change in NT-proBNP level from Visit 2 (baseline) to Visit 7 (day 90) using ANCOVA with the Visit 2 (baseline) value and randomization stratification factors as covariates. Local laboratory measures of NT-proBNP will be log-transformed for this analysis.

9.4.9.4 Changes in weight and Signs and Symptoms of Congestion

Weight and change in weight from baseline will be summarized at each scheduled visit by treatment group. A comparison between groups for the change from baseline to visit 7 will be analyzed using an ANCOVA model with terms for treatment arm and adjusted by the baseline value and randomization strata.

Ratings of severity for each HF sign and symptom will be assigned a score of 0-3. The distribution of responses at each visit as well as numeric summaries of scores and changes in scores will be summarized for dyspnea on exertion, orthopnea, edema, rales and jugular venous pulse. Treatment groups will be compared with respect to the changes in scores from Visit 2 to Visit 7 using the vanElteren test, an extension of the Wilcoxon rank sum test, stratified by randomization stratification factors.

9.4.9.5 Biomarkers

The analysis of central laboratory biomarker measurements will be described in a separate statistical analysis plan.

9.4.9.6 Event rates in Screen Failures

The Kaplan-Meier estimate of the cumulative event rate of 90-day all-cause mortality or HF readmission, and of each component of this composite, in the Screen Failure group, from the date of screen failure determination through 90 days following that date, will also be provided.

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 are 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

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Ethics Committee (EC)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the study participants, investigators, funding agency, the sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Ethics Committee and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, EC and/or competent authorities.

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 and genetic tests 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 or company supplying study test products 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.

With the participant's approval and as approved by local Ethics Committees (ECs), de-identified biological samples will be stored at the at a Biosample Repository with the same goal as the sharing of data with the Heart Initiative or its designees. These samples could be used to research the causes of heart failure, its complications and other conditions for which individuals with heart failure are at increased risk, and to improve treatment. The Biosample Repository will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the Heart Initiative.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

10.1.5.1 Principal Investigator

The Principal Investigator of the study is

Alexandre Mebazaa, MD PhD FESC
Hôpitaux Universitaires Saint-Louis-Lariboisière
University Paris Diderot
Inserm 942, Paris, France
alexandre.mebazaa@aphp.fr
mobile + 33 6 09 01 93 93

10.1.5.2 Medical Monitor

The Medical Monitor for the study is

Gad Cotter, MD
Momentum Research, Inc.
gadcotter@momentum-research.com
Tel +1(919)937-9157

10.1.5.3 Executive Committee

The Executive Committee will consist of at least three members and will be chaired by the Principal Investigator. The Executive Committee's role will be to supervise the overall conduct of the study, including amending the protocol where needed to protect the rights and welfare of study subjects or the scientific value of the study's findings. The committee will meet periodically throughout the study.

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including experience with HF clinical trials. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the Executive Committee.

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 electronic case report form (eCRF) 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. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the study is completed. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, or International Conference on Harmonisation Good Clinical Practice (ICH GCP). 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 at EudraCT, 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 the completion of the primary endpoint by contacting the Heart Initiative.

A publication committee consisting of several investigators and Sponsor representative(s) will solicit input and assistance from other investigators and will collaborate with authors and the Sponsor as defined in the Publication Charter. Membership on the committee does not guarantee authorship on any given publication; individual authors must be established criteria for authorship. 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

ACEi	Angiotensin converting enzyme inhibitor
AE	Adverse Event
AHF	Acute heart failure
ANCOVA	Analysis of Covariance
ARB	Angiotensin receptor blocker
ARNi	Angiotensin receptor neprilysin inhibitor
BIPAP	Bilevel Positive Airway Pressure
CHF	Chronic congestive heart failure
CMP	Clinical Monitoring Plan
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
COX-2	Cyclooxygenase-2
CP	Conditional power
CPAP	Continuous positive airway pressure
CRF	Case Report Form
CRT	Cardiac resynchonrization therapy
CV	Cardiovascular
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Forms
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
FAS	Full analysis set
FEV1	Forced expiratory volume during the first second
GCP	Good Clinical Practice
GDF-15	Growth differentiation factor 15
GLP	Good Laboratory Practices
GP	General practitioner
HF	Heart failure
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFSA	Heart Failure Society of America
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ITT	Intention-To-Treat
JVP	Jugular venous pulse
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease
MRA	Mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro B-type natriuretic peptide

PI	Principal Investigator
PPS	Per-protocol set
PTCI	Percutaneous transluminal coronary intervention
QA	Quality Assurance
QC	Quality Control
QoL	Quality of life
RAAS	Renin aldosterone angiotensin system
RCT	Randomized controlled trial
SAE	Serious Adverse Event
SAF	Safety set
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
TIA	Transient ischemic attack
WBC	White blood cells

10.3 PROTOCOL AMENDMENT HISTORY

Below is a summary of all Ethics Committee-approved versions of the protocol.

Version	Date	Description of Change	Brief Rationale
1.0	12-Jan-2018	Original version	N/A
2.0	11-Jun-2019	Amendment 1	Addition of 180-day follow-up; revision of primary endpoint to include all-cause rather than CV death; expansion of study beyond Europe.

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