[redacted]	**Statistical Analysis Plan**
	Sponsor: NOVARTIS **Protocol number: CRLX030A3301**

RLX030/Serelaxin

Clinical Trial Protocol CRLX030A3301 / NCT02064868

A multicenter, prospective, randomized, open label study to assess the effect of serelaxin versus standard of care in acute heart failure (AHF) patients

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Document History

Status and Version	Release Date	Change Description	Reason/Comment
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Final Version 2.0	27/02/2017	Second final release	Sponsor's approval

Authorization

The signatures on this page indicate review and approval of the Statistical Analysis Plan, version 2.0, dated 27/02/2017.

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LIST OF ABBREVIATIONS

ACE	Angiotensin-Converting Enzyme
ACS	Acute Coronary Syndrome
AE	Adverse Event
AHF	Acute Heart Failure
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBPDE	Confirmed Blood Pressure Decrease Event
CCU	Coronary Care Unit
cGMP	Current Good Manufacturing Practice
CI	Confidence Interval
CMQ	Customized MedDRA Query
COPD	Chronic Obstructive Pulmonary Disease
CRS	Case Retrieval Strategy
CRT	Cardiac Resynchronization Therapy
CSR	Clinical Study Report
CTT	Clinical Trial Team
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
DS&E	Novartis Drug Safety and Epidemiology Department
ECG	Electrocardiogram
eCRF	electronic Case Report Form
ED	Emergency Department
eDISH	evaluation of Drug-Induced Serious Hepatotoxicity
EF	Ejection Fraction
e.g.	Exempli Gratia
eGFR	Estimated Glomerular Filtration Rate
EMS	Emergency Medical Service(s)
ER	Emergency Room
EU	European Union
FAS	Full Analysis Set
GI	Gastrointestinal
HBA1c	Glycated hemoglobin
HDL	High Density Lipoprotein

HF	Heart Failure
HLGT	High Level Group Term
HR	Heart Rate
HRQoL	Health related Quality of Life
IABP	Intra-Aortic Balloon Pump
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICU	Intensive Care Unit
i.e.	Id Est
Inc.	Incorporation
IRT	Interactive Response Technology
ITT	Intent-To-Treat
IUD	Intrauterine Device
IUS	Intrauterine System
IV	Intra Venous
JVP	Jugular Venous Pulse
LA	Left Atrium
LDL	Low Density Lipoprotein
LOS	Length Of Stay
LV	Left Ventricular
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NC	North Carolina
NMQ	Novartis MedDRA Query
NT-proBNP	N-Terminal prohormone of Brain Natriuretic Peptide
NYHA	New York Heart Association
PD	Protocol Deviation
PO	Per Oral
PP	Per Protocol Set
PR	Pulse Rate
PVD	Patient Validation Document
RAN	Randomized Set
RBC	Red Blood Cell
RU	Resource Utilization
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SCR	Screened Set
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SMQ	Standard MedDRA Query

sMDRD	Simplified Modification of Diet in Renal Disease
SOC	Standard Of Care
TBL	Total Bilirubin
TP	Trial Programmer
TS	Trial Statistician
ULN	Upper Limit of Normal
USA	United States of America
VAS	Visual Analogue Scale
WBC	White Blood Cell
WHF	Worsening Heart Failure
WHO	World Health Organization

1. STUDY OBJECTIVES

1.1. PRIMARY OBJECTIVE

The primary objective of the study is to evaluate the effect of serelaxin as add-on therapy to standard of care (SOC) versus SOC alone in reducing in-hospital Worsening Heart Failure (WHF) requiring rescue therapy or all cause death, from randomization through Day 5.

1.2. SECONDARY OBJECTIVES

The secondary objectives of the study are the following:

- To assess the effect of serelaxin as add-on therapy to SOC versus SOC alone in reducing in-hospital WHF requiring rescue therapy or all cause death or readmission for heart failure, from randomization through Day 14.
- To assess the effect of serelaxin as add-on therapy to SOC versus SOC alone in reducing the number of patients with persistent symptoms or signs of Heart Failure (HF) / not showing an improvement versus baseline conditions from randomization through Day 5 (persisting need of IV therapy for HF).
- To evaluate the effect of serelaxin as add-on therapy to SOC versus SOC alone in reducing the rate of renal deterioration (defined as ≥ 0.3 mg/dL increase in serum creatinine), from randomization through Day 5.
- To evaluate the effect of serelaxin as add-on therapy to SOC versus SOC alone in modifying the index length of stay (LOS) by location (e.g., ICU, CCU, cardiology department) in days and hours (ICU).
- To evaluate the safety and tolerability of intravenous serelaxin in Acute Heart Failure (AHF) patients during a period of 30 days following exposure.
- To collect data on health-related quality of life (HRQoL) and economic burden to provide a more comprehensive analysis of the burden of HF, beyond the clinical outcomes.

[redacted]

[redacted]

2. BACKGROUND/INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to detail the planned analyses for the clinical study report (CSR) for study CRLX030A3301.

2.1. STUDY DESIGN

This study is a prospective, multinational, multicenter, randomized, open label clinical trial to evaluate the efficacy, safety and tolerability of serelaxin as add-on therapy to SOC versus SOC alone in AHF subjects in the primary composite end-point of in-hospital WHF or all cause deaths through Day 5. The outcome defined as in-hospital WHF (with signs/symptoms of worsening conditions, requiring therapy intensification) is adjudicated by an Independent Board.

After signing an Ethics Committee or Institutional Review Board approved Informed Consent Form, subjects are asked to undergo screening procedures for study eligibility. It is essential that the screening is completed in time to allow the randomization within 16 hours from presentation. Investigators are invited to initiate the serelaxin treatment as soon as possible after randomization.

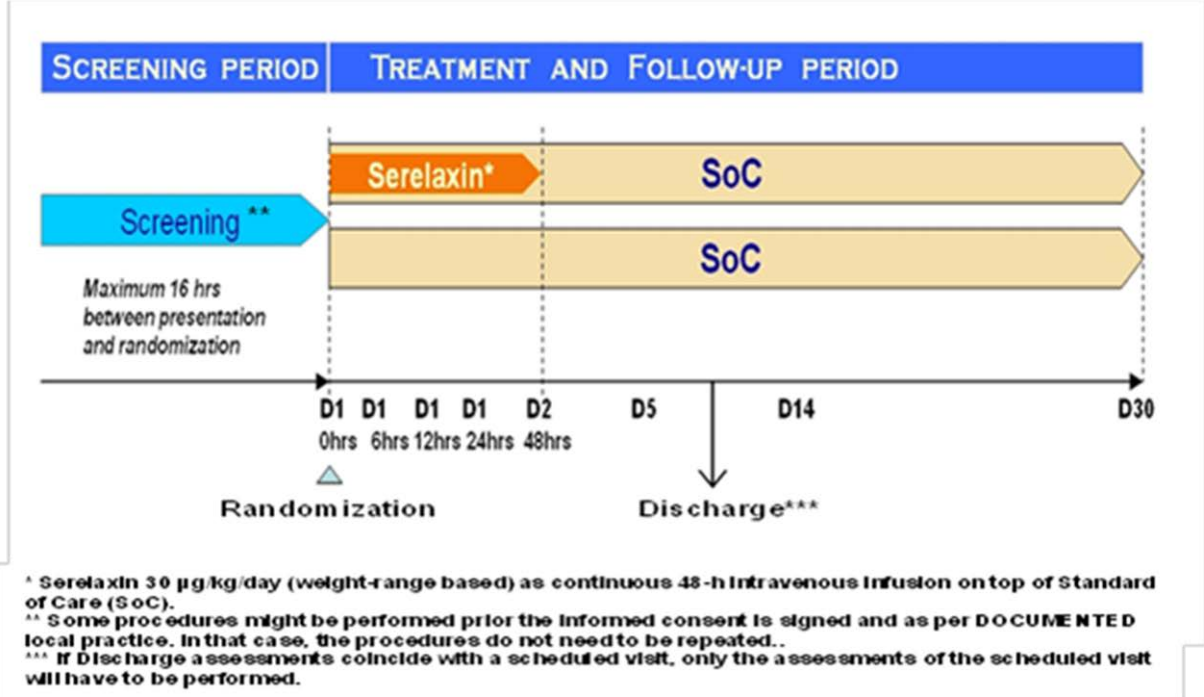
After assessing patient eligibility during the screening period, patients who meet the study inclusions and none of the exclusion criteria are randomized in a 2:1 ratio to receive intravenous infusion of either serelaxin for up to 48 hours in addition to SOC or SOC alone.

Presentation starts as the earliest of (1) time of presentation at either the ER/ED, ICU/CCU or ward (excludes EMS or other pre-hospital care); or (2) time of first IV loop diuretic for treatment of the current AHF episode prior to arrival at the hospital (this includes outpatient clinic, ambulance, or hospital including emergency department).

Serelaxin treatment will begin as soon as possible after randomization; it is administered via continuous intravenous (IV) infusion for 48 hours according to a weight-range adjusted dosing regimen at the nominal dose of 30 µg/kg/day. Due to the potential risk of hypotension, blood pressure is monitored regularly during the administration of study drug.

The study includes a short-term follow-up through Day 5, discharge and through Day 14, and an extension follow-up period up to Day 30, when all subjects receive a phone call to ascertain vital status and the need for repeated hospitalization.

Figure 2.1-1: Study design



* Serelaxin 30 µg/kg/day (weight-range based) as continuous 48-h intravenous infusion on top of Standard of Care (SoC).
** Some procedures might be performed prior the informed consent is signed and as per DOCUMENTED local practice. In that case, the procedures do not need to be repeated..
*** If Discharge assessments coincide with a scheduled visit, only the assessments of the scheduled visit will have to be performed.

In addition to the core study, the following sub-studies are planned:

- [redacted]
- [redacted]
- [redacted]

The analyses of these sub-studies will be described in a separate SAP for each sub-study.

2.2. TREATMENT GROUPS AND RANDOMIZATION

Subjects are randomized in a 2:1 ratio to receive one of the following:

- Serelaxin (30 µg/kg/day) as continuous 48-hour intravenous infusion plus standard of care.
- Standard of care only.

At baseline, all eligible patients who fulfill all inclusion/exclusion criteria are randomized via Interactive Response Technology (IRT) to one of the treatment arms.

The IRT assigns a randomization number to the patient, which links the patient to a treatment arm, and specifies a unique medication number (for patients randomized to serelaxin only) for the first package of investigational treatment to be dispensed to the patient. The randomization number is not communicated to the caller.

The randomization numbers are generated using the following procedure to ensure an unbiased treatment assignment. A patient randomization list is produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers (for serelaxin arm only). A separate medication list is produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug.

Mis-randomized patients are those who have not been qualified for randomization, have been inadvertently randomized into the study and who did not take study drug. Mis-randomized patients are defined as cases where IRT calls were made by the site either prematurely or inappropriately prior to confirmation of the patient's final randomization eligibility and administration of serelaxin, when applicable, was not performed. These patients should have been considered screen failures as they did not meet eligibility criteria and should subsequently be discontinued from the study. Sites should notify IRT and contact their Novartis monitor as soon as possible if a patient is mis-randomized into the study.

2.3. STUDY POPULATION

Similarly to the RELAX-AHF study, subjects are selected among patients who have been admitted with AHF, who have normal to elevated blood pressure (SBP ≥ 125 mmHg at the start and at the end of the screening period) and have impaired renal function defined as an eGFR ≥ 25 and ≤ 75 ml/min/1.73m^2 at screening (calculated using the sMDRD equation).

The study plans to randomize approximately 3,183 patients in approximately 450 study sites mainly in Europe.

Inclusion criteria

Subjects must fulfill all of the following criteria at screening to be eligible for the study. The screening period is defined as the interval that begins at the time the informed consent is signed and ends with the qualification of the subject for entry into the study (i.e., when subject has met all eligibility criteria):

1. Able to provide written informed consent before any study-specific assessment is performed. The AHF diagnosis assessments performed as per current local institution/hospital standard practice or as part of routine clinical care can be used to support patient screening even if performed before obtaining informed consent.
2. Male or female ≥ 18 years of age with body weight ≥ 40 Kg and ≤ 160 Kg.

3. Systolic blood pressure ≥ 125 mmHg at the beginning of the screening period (after ICF signature) and at the end of the screening period (prior to randomization).
4. Admitted/hospitalized for AHF. AHF is defined as including all of the following measured at any time between presentation and the end of screening:
    - Persistent dyspnea at rest or with minimal exertion, at screening and at the time of randomization, despite standard background therapy for acute decompensated heart failure including intravenous furosemide of at least 40 mg total (or equivalent)
    - Pulmonary congestion assessed through physical examination and chest X-Ray obtained during routine clinical practice at any time between presentation and the end of screening (prior to randomization)
    - N-terminal pro B-type natriuretic peptide (NT-proBNP) ≥ 2,000 pg/mL or BNP ≥ 500 pg/mL. For patients treated with valsartan/sacubitril (Entresto®), BNP is not suitable and only NT-pro-BNP should be assessed.
5. Able to be randomized **within 16 hours** from presentation to the hospital [presentation starts as the earliest of (1) time of presentation at either the ER/ED, ICU/CCU or ward; or (2) time of first IV loop diuretic for treatment of the current AHF episode prior to arrival at the hospital] (this includes outpatient clinic, ambulance, or previous hospital including emergency department).
6. Received intravenous furosemide of at least 40 mg (or equivalent) at any time between presentation and the start of screening for the study.
7. Impaired renal function defined as an estimated glomerular filtration rate (eGFR), between presentation and randomization of ≥ 25 and ≤ 75 mL/min/1.73 m^2, calculated using the simplified Modification of Diet in Renal Disease (sMDRD) equation (Levey AS et al., 2007; Myers GL et al., 2006).

Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in the study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients:

- Dyspnea primarily due to non-cardiac causes, such as acute or chronic respiratory disorders or infections (i.e., severe chronic obstructive pulmonary disease, bronchitis, pneumonia), or primary pulmonary hypertension sufficient to cause dyspnea at rest, which may interfere with the ability to interpret the primary cause of dyspnea.
- Known history of respiratory disorders requiring the daily use of IV steroids (does not include inhaled or oral steroids) at least 2 months prior to randomization; need for intubation or the current use of IV steroids for COPD.

- Patients with blood pressure > 180 mmHg at the end of screening or persistent heart rate > 130 bpm.
- Temperature > 38.5°C (oral or equivalent) or sepsis or active infection requiring IV anti-microbial treatment.
- Current (within 2 hours prior to randomization) or planned (through the completion of study drug infusion) treatment with any IV vasoactive therapies, including vasodilators (including nesiritide), positive inotropic agents and vasopressors, or mechanical support (intra-aortic balloon pump, endotracheal intubation, assisted (invasive or non-invasive) ventilation, or any ventricular assist device, or ultrafiltration, hemofiltration or dialysis), with the exception of IV furosemide (or equivalent diuretic) or IV nitrates at a dose of ≤ 0.1 mg/kg/hour if the patient has a systolic BP > 150 mmHg at the start of the screening.
- Significant left ventricular outflow obstruction, uncorrected, such as obstructive hypertrophic cardiomyopathy or severe aortic stenosis (i.e., aortic valve area < 1.0 cm^2 or mean gradient > 50 mmHg on prior or current echocardiogram), severe aortic regurgitation and severe mitral stenosis.
- Clinical evidence of acute coronary syndrome currently or within 30 days prior to enrollment. (Note that the diagnosis of acute coronary syndrome is a clinical diagnosis and that the sole presence of elevated troponin concentrations is not sufficient for a diagnosis of acute coronary syndrome, given that troponin concentrations may be significantly increased in the setting of AHF).
- AHF due to significant arrhythmias, which include any of the following: sustained ventricular tachycardia, bradycardia with sustained ventricular rate < 45 beats per minute or atrial fibrillation/flutter with sustained ventricular response of > 130 beats per minute.
- Women of child bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study treatment and for 5 days after cessation of study drug. Highly effective contraceptive methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

- Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
- Combination of any two of the following (a+b, or a+c, or b+c):
    a) Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception
    b) Placement of an intrauterine device (IUD) or intrauterine system (IUS)
    c) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive local laboratory test.
- Acute myocarditis or hypertrophic obstructive, restrictive, or constrictive cardiomyopathy (does not include restrictive mitral filling patterns seen on Doppler echocardiographic assessments of diastolic function).
- Major surgery, including implantable devices (e.g., ICD, CRT), or major neurologic event including cerebrovascular events, within 60 days prior to screening.
- History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past year.
- Hematocrit < 25% or a history of blood transfusion within the 14 days prior to screening or active, life-threatening GI bleeding.
- Known hepatic impairment or AST / ALT > 3 ULN.
- Known presence of active or recurrent bacterial, fungal or viral infection at the time of enrollment.

- Any organ transplant recipient, or patient currently listed for imminent transplant (i.e., do not exclude patients on an administrative transplant waiting list), or admitted for any transplantation.
- Any other medical conditions that may put the patient at risk or influence study results in the investigator's opinion, or that the investigator deems unsuitable for the study, including drug or alcohol abuse or psychiatric, behavioural or cognitive disorders, sufficient to interfere with the patient's ability to comply with the protocol instructions or follow-up procedures.
- Administration of any investigational drug or implantation of investigational device, or participation in another trial, within 30 days before screening or previous treatment with serelaxin.
- Inability to follow instructions or comply with follow-up procedures.
- Known hypersensitivity to serelaxin or similar substances or to any of the excipients.

2.4. STUDY DRUG AND DOSING

Serelaxin is administered according to a weight-range adjusted dosing regimen at a nominal dose of 30 µg/kg/day, as a continuous intravenous infusion for 48 hours.

The study drug is provided as a 1 mg/mL solution in 6 mL vials (with 3.5 mL fill). For the randomized patients to receive the study drug infusion, it can be withdrawn from the vials contained in the kits, injected into a 250 mL intravenous bag of 5% dextrose solution and then infused through a dedicated IV line or port, using compatible tubing, infusion filters and IV bags according to instructions in the Pharmacy Manual.

Each study site is supplied by Novartis with investigational treatment in kits containing 1 vial of serelaxin each, enough study drug for 24 hours of infusion (for all patients < 115 kg in body weight). At randomization time, the IRT specifies the first package of investigational treatment to be dispensed to the patient; to receive the study drug for the second 24 hours of infusion, the investigator's staff contacts the IRT again and requests a second kit (for patients randomized to serelaxin only). In case the subject is ≥ 115 kg in body weight, two study drug kits are assigned via IRT for each 24 hour of infusion.

Table 2.4-1: Weight-range adjusted dosing regimen of serelaxin

Body weight (kg)	Serelaxin (mg)	Volume of serelaxin to be added to 250 mL IV bag of sterile 5% dextrose for intravenous infusion over a period of 24 hours
40-59 kg	2.0 mg	2.0 mL
60-74 kg	3.0 mg	3.0 mL
75-114 kg	3.5 mg	3.5 mL
115-160 kg	5.5 mg	5.5 mL (2 vials needed)

All kits of investigational treatment assigned by the IRT will be recorded in the IRT.

Due to the potential risk of hypotension, blood pressure is monitored regularly during the administration of study drug. If at any time during dosing, the subject's systolic blood pressure decreases by > 40 mm Hg from just before the study drug infusion but is ≥ 100 mmHg in 2 consecutive measurements 15 minutes apart, serelaxin infusion rate is decreased by 50% for the remainder of the 48 hour study drug administration. Serelaxin administration is permanently discontinued at any time if in 2 consecutive measurements, 15 minutes apart, systolic blood pressure is reduced to < 100 mmHg. In addition, dosing may be discontinued at any time at the discretion of the investigator. Reasons the investigator may discontinue study drug administration include, but are not limited to, serious or intolerable adverse events (AEs) suspected to be related to study drug. If dosing is discontinued for hypotension or any safety reasons, re-administration of study drug is not allowed. For non-safety reasons (problems with the infusion line, etc.), dosing may be interrupted once for each patient for up to 1 hour. Time from initiation of study drug infusion to completion must not exceed 48 hours (i.e., if the infusion is interrupted or delayed, it must be terminated after 48h from the start, regardless of the actual infusion time). In the event that study drug administration is discontinued for any reason, the patient will continue to be followed at all study visits defined in the protocol.

No additional treatment beyond investigational treatment is requested for this trial. All patients are required to receive standard of care background HF management during the study, according to local guidelines/international standards. This treatment can include but is not limited to intravenous and/or oral diuretics, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor antagonists, β blockers and aldosterone receptor antagonists, etc.

2.5. SAMPLE SIZE

The primary end point of the study is the time to in-hospital adjudicated outcome Worsening of Heart Failure (WHF) requiring intensification of therapy, or all cause death through Day 5 post randomization.

[redacted]

[redacted]

2.6. SCHEDULE OF TIME AND EVENTS

Each patient is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject Number will not be reused. Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator.

The patient is followed up to Day 30 and relevant information is entered into the eCRF.

Table 2.6-1 lists all of the assessments and indicates with an ‘‘x’’ when the visits are to be performed.

Patients shall be seen daily through index hospitalization until Day 5, until discharge (whichever occurs first), and then at Day 14. If for any good reason, the assessments at Day 5 cannot be done on the designated day, a window of + 1 day is allowed. A “visit window” of +/- 2 days is allowed for Day 14 and for phone contact on Day 30.

Patients should be seen for all visits on the designated day or timepoint, or as close to it as possible. Patients are expected to return to the clinic for all scheduled study visits. Patients unable or unwilling to return to the hospital/clinic for scheduled visits will be contacted by telephone as close as possible to the expected visit to obtain information about survival status.

Patients who prematurely discontinue the investigational treatment will remain in the study and shall undergo all the assessments illustrated in Table 2.6-1. If a patient withdraws from participation in the study, or refuses to return for study assessments, or is unable to do so, every effort shall be made to contact them or a knowledgeable informant by telephone and/or other measures to determine the patient's survival status during the follow-up period.

Table 2.6-1: Assessment schedule

Visit number	0	0-1	1-1	1-2	1-3	1-4	1-5	1-6	2		3	4
Time of Visit	Screening	End of Screening/ Baseline	6h	12h	24h	48h	D3	D4	D5[12]	Discharge[13]	D14 (± 2)	D30 (± 2)
Phase			Drug Infusion[0]				Post-treatment daily assessment				Follow-up	
Obtain Informed Consent	X											
Demographic data	X											
Inclusion/Exclusion criteria	X											
Medical history, including diagnostic of AHF, Alcohol, drug abuse, education level, living arrangement and smoking histories	X											
Physical examination with vital signs[1]	X		X	X	X	X	X	X	X	X	X	
Height	X											
Body weight measurement[1]	X				X	X	X	X	X	X	X	
Physician assessment of signs and symptoms of HF[1]		X	X	X	X	X	X	X	X	X	X	
Worsening Heart Failure (WHF)[2]			X	X	X	X	X	X	X	X	X	
ECG	X								X	X		
Chest X-Ray[3]	X											
BP and HR measurements[4]	X	X	X	X	X	X	X	X	X	X	X	
NT-pro-BNP or BNP for study entry[5]	X											
Serum cTnT or cTnI[6] for study entry	X											
Pregnancy test[6]	X											
eGFR (MDRD)[6]	X					X			X	X		
Laboratory tests (Local Laboratory)[6,7]	X				X	X			X	X	X	
[redacted]		X				X			X			
		X				X			X			
[redacted]		X			X	X			X			

[redacted]		X				X			X			
HRQoL questionnaire (EQ-5D-5L)		X				X			X	X	X	
Healthcare Resource Utilisation[9]		X	X	X	X	X	X	X	X	X	X	X
Contact IRT[10]	X	X			X							
Administer study medication		X→										
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Non-serious Adverse Events[11]	X	X	X	X	X	X	X	X	X	X		
Serious Adverse Event[11]	X	X	X	X	X	X	X	X	X	X	X	X
Vital Status									X	X	X	X

[0] Study drug will be administered as an IV infusion for 48 hours. If at any time during dosing, the subject's systolic blood pressure is decreased by > 40 mm Hg from baseline but is ≥ 100 mm Hg in 2 consecutive measurements 15 minutes apart, the study drug treatment infusion rate will be decreased by 50% for the remainder of the study drug administration. If at any time during dosing, the subject's systolic blood pressure is < 100 mm Hg in 2 consecutive measurements 15 minutes apart, the study drug infusion will be terminated.

[1] Physical examination includes assessment of vital signs. Following randomization, all physical examinations should be performed daily at approximately the same time of day. Daily vital signs may be measured and recorded by trained study personnel as well as trained healthcare personnel as part of their routine clinical duties. For details of assessment see Section 6.5.1, Section 6.5.2 of the Study Protocol.

[2] WHF is defined as worsening signs and/or symptoms of heart failure that require an intensification of intravenous therapy for heart failure or mechanical ventilation or circulatory support. Such treatment can include the institution or up-titration of IV furosemide, IV nitrates or any other IV medication for heart failure or institution of mechanical support such as assisted (invasive/non-invasive) ventilation, IABP, etc.

[3]Chest X-Ray is not considered a study-related procedure. It should be done according to local diagnostic practice. Patients may only enter the trial with pulmonary congestion on a chest X-Ray obtained during routine clinical practice at any time between presentation and the end of screening (prior to randomization). If the chest X-Ray from routine clinical assessments is not available, the patient may not enter the trial.

[4] BP and HR measurements should be performed for all patients at the beginning of the screening period (after ICF signature) and at the end of the screening period (prior to randomization). For serelaxin patients, frequent BP and HR measurements should be performed between randomization and immediate start of study drug administration, 30 and 60 minutes after start of study drug administration, then every hour for the first 6 hours and then every 3 hours during study drug infusion, including night time hours. Post-infusion, BP and HR should be measured every 3 hours until 12 hours following end of infusion, then every 6 hours for 48 hours and then every 24 through the index hospitalization, at discharge, at Day 5 and then at Day 14.For patients randomized to the SOC group, BP and HR measurements should be performed at 6, 12, 24, 48 hours post-randomization, daily through the index hospitalization, at discharge, at Day 5 and then at Day 14. All measurements should be performed as close as possible to specified time points. BP and HR should be measured with the patient in the same position and with the same equipment using the same arm. These measurements may be made and recorded by trained study personnel, as well as trained healthcare personnel as part of their routine clinical duties,

[5] Measured through a point of care device provided by Sponsor required only if the site is not able to obtain local lab test results within the 16-hour timeframe or if local lab does not offer it at all.

[6] Measured at local laboratory. Following randomization, local laboratory collections can be adjusted to conform to the hospital's routine laboratory collection schedule and can be collected at any time of the day.

[7] Clinical laboratory tests include hematology and chemistry and will be performed locally. Urinalysis will be conducted at baseline, 24 and 48 hours only to rule out any conditions that might be requiring further diagnostic evaluation or treatment. See Section 6.5.4 for details of the Study Protocol.

[redacted]

[9] Throughout the index hospitalization, the level of healthcare resource utilization shall be assessed by the overall length of stay, length of time in specific inpatient care units and procedures rendered during hospital stay. There may be circumstances when the collection of the data after completion of the study may be warranted.

[10] Investigational treatment kits containing 1 vial of serelaxin each is enough for 24 hours of study infusion. To receive the second 24 hours of study drug, the investigator's staff will contact the IRT again and request a second kit. For SOC patients, the contact with IRT at Visit 1-3 is not necessary.

[11] Non-serious Adverse Events will be collected through Day 5 and all Serious Adverse Events will be collected through Day 14,

regardless of suspected causality. After Day 14, only suspected Serious Adverse Events will be collected and databased.

[12] If for any good reason, the assessments at Day 5 cannot be done in the designated day, a window of + 1 day is allowed.

[13] If discharge assessments coincide with a scheduled visit, only the assessments of the scheduled visit will have to be performed. If discharge occurs at any time after Day 5, all discharge assessments have to be performed.

[redacted]

3. POPULATIONS OF ANALYSIS

Analysis population

Patients without a valid or adequately obtained Informed Consent Form (ICF) will be excluded from any analysis population.

The following analysis populations are defined:

- **Screened set (SCR)**: all patients who signed the informed consent.
- **Randomized set (RAN):** all patients who received a randomization number, regardless of receiving trial medication and including mis-randomized patients.
- **Full analysis set (FAS):** all randomized patients who were not mis-randomized. Following the intent-to-treat (ITT) principle, patients will be analyzed according to the treatment they have been assigned to at randomization. Mis-randomized patients are those who have not qualified for randomization, have been inadvertently randomized into the study but who did not enter the treatment phase and who did not receive serelaxin. Mis-randomized patients are defined as cases where randomizations were made by the site either prematurely or inappropriately prior to confirmation of the patient's final randomization eligibility. These patients should subsequently be discontinued from the study.
- **Per Protocol set (PP):** all patients in the FAS without major protocol deviations, as defined in the Patient Validation Document (PVD).
- **Safety set (SAF)**: all patients who received any amount of study treatment or standard of care treatment and who have at least one post-baseline safety assessment. Of note, the statement that a patient had no adverse events also constitutes a safety assessment. Patients will be analyzed according to treatment received.

Protocol deviation

The protocol deviation concerning the mis-randomization will be detected during the course of the study and reported by means of the specific tool developed on eCRF.

All cases of prospectively defined protocol deviations (PD) will be identified prior to clinical database lock/unblinding and entered into a dedicated data panel as part of the locked database. Certain deviations may stipulate that data collected from the subjects will be excluded from analysis population(s). All exceptional cases, problems and the final decisions on the allocation of subjects to populations will be fully defined, documented and approved by the Novartis study team before data base lock (in particular before breaking the blind where applicable) and will be fully identified and summarized in the Patient Validation Document. The major protocol deviations resulting in exclusion of subjects from an analysis population are outlined in the table below:

Table 3-1: Deviations resulting in exclusion of subjects from analysis populations

	Deviation		Exclusion from analysis set				
Category	**Description**	**Code(s) ***	**SCR**	**RAN**	**FAS**	**PP**	**SAF**
Selection criteria not met	Lack of written informed consent (Inclusion criteria #1)	IC001 IC001_A1	X	X	X	X	X
	Systolic blood pressure <125 mmHg at the beginning and at the end of the screening period (Inclusion criteria #3)	IC003 IC003_M1				X	
	Patient hospitalized for reasons of non-AHF event (Inclusion criteria #4)	IC004 IC004_M1 IC004_A1				X	
	Lack of randomization within 16 hours from presentation to the hospital (Inclusion criteria #5)	IC005 IC005_M1				X	
	Lack of intravenous furosemide of at least 40 mg (or equivalent) at any time between presentation and the start of screening for the study (Inclusion criteria #6)	IC006 IC006_M1				X	
	Lack of impaired renal function defined as eGFR between presentation and randomization of ≥ 25 and ≤ 75 mL/min/1.73 m^2 (Inclusion criteria #7)	IC007 IC007_M1				X	
	Persistent dyspnea at rest or with minimal exertion, at screening and at the time of randomization, despite standard background therapy for acute decompensated heart failure including intravenous furosemide of at least 40 mg total (or equivalent) (Exclusion criteria #1)	EC001 EC001_M1				X	
	Known significant pulmonary disease (obsolete exclusion criteria of original protocol)	EC005 EC006				X	
	Patients with systolic blood pressure >180 mmHg at the end of screening or persistent heart rate >130 bpm (Exclusion criteria #3)	EC034				X	
	Sepsis or active infection requiring IV anti-microbial treatment (Exclusion criteria #4)	EC003				X	
	Current or planned treatment with any IV vasoactive therapies or mechanical support, with the exception of IV furosemide (or equivalent diuretic) or IV nitrates at a dose of ≤0.1 mg/kg/hour if the patient has a SBP >150 mmHg at the start of the screening (Exclusion criteria #5)	EC004 EC004_M1 EC004_A1 EC004_M2				X	
	Significant left ventricular outflow obstruction, uncorrected, such as obstructive hypertrophic cardiomyopathy or severe aortic stenosis severe aortic regurgitation and severe mitral stenosis (Exclusion criteria #6)	EC007 EC008_M1 EC009_M1 EC010_M1				X	
	Clinical evidence of acute coronary syndrome currently or within 30 days prior to enrollment. (Exclusion criteria #7)	EC011				X	
	AHF due to significant arrhythmias, which include any of the following: sustained ventricular tachycardia, bradycardia with sustained ventricular rate <45 beats per minute or atrial fibrillation/flutter with sustained ventricular response of >130 beats per minute (Exclusion criteria #8)	EC012 EC013 EC014				X	

Deviation			Exclusion from analysis set				
Category	**Description**	**Code(s) ***	**SCR**	**RAN**	**FAS**	**PP**	**SAF**
Treatment deviation	Drug infusion not administered according to a weight-range adjusted dosing regimen at the nominal dose of 30 µg/kg/day.	DRUG02 DRUG02_A3 DRUG03				X	
	Study drug not injected into a 250 mL intravenous bag of 5% dextrose solution or not infused through a dedicated IV line or port, using compatible tubing, infusion filters and IV bags or not following instructions in the Pharmacy Manual.	DRUG05				X	
	Investigational treatment not handled and stored properly (including temperature control).	DRUG06				X	
	Expired investigational treatment	DRUG07				X	
	Serelaxin infusion began later than 4 hours after start of study drug preparation.	DRUG011				X	
	Serelaxin administered despite patient randomized in SOC arm	DRUG12				X	
	Serelaxin administered despite patient not randomized with IRT	DRUG13		X	X	X	
	Serelaxin not administered despite patient randomized in Serelaxin arm and SBP pre-infusion ≥ 100 mmHg.	DRUG14				X	X
Other	Subject does not undergo any clinical evaluations of AHF signs/symptom and subject does not report any information about the need for further IV or oral HF treatment and about the occurrence of worsening HF events through Day 5	PROC03				X	
	Subject does not perform the scheduled visit at Day 5	PROC03_A1				X	
	Subject not randomized but entered the treatment phase	PROC06		X	X	X	
	Subject mis-randomized (i.e. subject who has not been qualified for randomization, has been inadvertently randomized into the study, who did not enter the treatment phase and who did not undergo Serelaxin administration)	PROC07			X	X	X

* Deviations codes as defined in the Protocol Deviation Handling Document (blind & unblind). Codes could possibly change before database lock.

In addition, deviations not defined in the protocol resulting in exclusion of subjects from an analysis population are outlined in the table below.

Table 3-2: Non-protocol deviations resulting in exclusion of subjects from analysis populations

Non-Protocol Deviation		Exclusion from analysis set				
Category	**Description**	**SCR**	**RAN**	**FAS**	**PP**	**SAF**
Non-protocol deviation	Subject has no post-baseline safety assessment.					X

Non-Protocol Deviation		Exclusion from analysis set				
Category	**Description**	**SCR**	**RAN**	**FAS**	**PP**	**SAF**
Non-protocol deviation	Subject randomized to Serelaxin group but not receiving any dose of study medication				X	X

4. VARIABLES

4.1. EFFICACY PARAMETERS

Primary efficacy parameter

Worsening of Heart Failure/all cause death through Day 5

The primary efficacy variable of the study is the time to in-hospital Worsening of Heart Failure (WHF) requiring rescue therapy or all cause death through Day 5 post randomization.

In-hospital WHF through Day 5 post randomization includes worsening signs and/or symptoms of heart failure that require an intensification of intravenous therapy for heart failure or mechanical ventilation, renal or circulatory support. Such treatment can include the institution or uptitration of IV furosemide, IV nitrates or any other IV medication for heart failure, or institution of mechanical support such as assisted (invasive or non-invasive) ventilation, ultrafiltration, haemodialysis, intra-aortic balloon pump or ventricular assist device, etc. This endpoint also includes patients who die in this 5-day period of any cause before experiencing episode(s) of WHF.

A central event adjudication committee is appointed to oversee the WHF primary endpoint adjudication.

Relevant evaluations to detect in-hospital WHF are performed in the serelaxin arm at 6, 12, 24 and 48 hours from start of study drug infusion, daily through index hospitalization, at Day 5 and discharge, and then at Day 14. For patients in the SOC arm, relevant evaluations are performed at 6, 12, 24 and 48 hours from randomization, daily through index hospitalization, at Day 5 and discharge, and then at Day 14.

Death information is collected in a dedicated eCRF section.

Secondary efficacy parameters

In-hospital Worsening of Heart Failure/all cause death/hospital readmission for HF through Day 14

The secondary efficacy endpoint is time to worsening HF requiring rescue therapy as defined above, or all cause death, or hospital readmission for heart failure through Day 14 post randomization.

Relevant evaluations to detect in-hospital WHF are performed in the serelaxin arm at 6, 12, 24 and 48 hours from start of study drug infusion, daily through index hospitalization, at Day 5 and discharge, and then at Day 14. For patients in the SOC arm, relevant evaluations are performed at 6, 12, 24 and 48 hours from randomization, daily through index hospitalization, at Day 5 and discharge, and then at Day 14.

Death and re-hospitalization information are collected in dedicated eCRF sections.

Persistent signs and symptoms of HF/non-improvement

The number of patients with persistent symptoms or signs of HF / not showing an improvement versus baseline conditions through Day 5 (persisting need of IV therapy for HF) will be evaluated.

Patients with persistent symptoms or signs of HF / not showing an improvement versus baseline conditions through Day 5 are those patients who take any IV therapy for HF at each assessment time point as reported in the eCRF sections “IV Loop Diuretic Medication for Heart Failure” and “IV Medications Other than Loop Diuretics”.

Moreover, the investigator or appropriate qualified designee evaluates the symptoms and signs of heart failure, including dyspnea on exertion or at rest, orthopnea, rales, jugular venous pulse (JVP) and peripheral edema. These evaluations are performed at baseline, 6, 12, 24 and 48 hours from start of study drug infusion, daily through index hospitalization, at Day 5, at discharge and then at Day 14 for the serelaxin arm. For patients in the SOC arm, relevant evaluations are performed at baseline, at 6, 12, 24 and 48 hours from randomization, daily through index hospitalization, at Day 5, at discharge, and then at Day 14.

These evaluations should be done at approximately the same time of the day, each day, in the same position and hospital/clinic setting, preferably by the same assessor.

Renal deterioration

Renal deterioration is defined as an increase of ≥ 0.3 mg/dL from screening in serum creatinine levels. Rate of renal deterioration at 24 hours, at 48 hours, at Day 5, at discharge, and at Day 14 post randomization will be evaluated.

Serum creatinine evaluations are performed locally at screening, at 24 and 48 hours, at Day 5, at discharge, and then at Day 14 post randomization.

Index length of hospital stay

Index length of hospital stay (in hours) is defined as the index hospitalization discharge date and time minus the index hospitalization admission date and time + 1 minute.

Index length of hospital stay, from admission to discharge, will be evaluated by location (emergency ward, emergency care unit, etc.).

Index hospitalization details are collected in eCRF at Screening, Day 5, discharge visit, Day 14 and Day 30 post randomization.

Death through Day 30

All deaths (adjudicated or not) occurring from randomization through Day 30 will be used in the analysis.

Re-hospitalization post-discharge

The number of re-hospitalizations per patient post-discharge will be described.

The time to first re-hospitalization (in days) will be defined as the first re-hospitalization admission date minus the randomization date + 1 day.

Health-related Quality of Life

The EQ-5D-5L is a widely used, self-administered questionnaire designed to assess health status in adults. The measure is divided into two distinct sections. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). The second section of the questionnaire measures self-rated (global) health status utilizing a vertically oriented visual analogue scale where 100 represents the “best possible health state” and 0 represents the “worst possible health state”.

In this study, the first administration of the EQ-5D-5L questionnaire occurs at baseline visit. If, for whatever reason, the patient is not able to fill in the questionnaire at baseline, it is possible to collect retrospectively these data on Day 2. If this is the case, on Day 2, two questionnaires need to be filled in at this visit: the first one asking the patient to retrospectively describe how he/she felt on the day of admission, and the second one asking the patient to describe how he/she feels today. A special permission was provided by EuroQoL for the use with 2-day recall of the questionnaire.

The EQ-5D-5L quality of life assessment is completed by all study patients (both serelaxin and SOC groups) at baseline (i.e., randomization), at Day 2, at Day 5, at discharge, and at Day 14 post randomization.

Resource utilization

Analyses will be undertaken, as appropriate, to assess the effects of treatments on healthcare resource utilization (RU) parameters.

Throughout the index hospitalization, the level of healthcare resource utilization shall be assessed by the overall length of stay, length of time in specific inpatient care units and procedures rendered during hospital stay. In addition, number of re-hospitalizations (events), number of patients with 1, 2, 3 re-hospitalization(s) and time to first (and recurrent) re-hospitalization(s) (in days) will be evaluated.

Moreover, the details about emergency/urgent care >24 hours not resulting in admission, including tests performed, will be provided.

Data for a health economic analysis are collected from eCRFs, most notably Hospital Discharge, Re-hospitalization and Death. Data on emergency/urgent care >24 hours not resulting in admission are collected in dedicated eCRF sections. Data on medical resource use are collected

for all enrolled patients from the index hospitalization at Day 5, at discharge, and then at Day 14, and through phone contact at Day 30 post randomization.

[redacted]

4.2. SAFETY PARAMETERS

Adverse Events (AEs) / Serious Adverse events (SAEs)

All adverse events are collected through Day 5, and all serious adverse events are collected through Day 14, regardless of suspected causality. After Day 14, only suspected related serious adverse events are collected and entered in the eCRF.

Adverse events are recorded in the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information: the severity grade (mild/moderate/severe); its relationship to the study treatment (no; yes; yes, investigational treatment; yes, other study treatment (not investigational); yes, both and/or indistinguishable); its duration (start and end dates and times); whether it constitutes a serious adverse event (SAE); action taken regarding investigational treatment; whether other medication or therapies have been taken (concomitant medication or non-drug therapy); its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; unknown).

Each pregnancy occurring to a subject involved in the trial is reported as an Adverse Event on the eCRF.

Vital signs

Height in centimeters (cm) or inches (inch) is measured at screening only.

Body weight (to the nearest 0.1 kilogram [kg] or 0.1 pound [lb] in indoor clothing, but without shoes) is measured at Screening and at 24 and 48 hours after study drug infusion in the

serelaxin arm / at 24 and 48 hours after randomization in SOC arm, and daily through index hospitalization, at Day 5, at discharge, and then at Day 14. These measurements during hospitalization can be performed at any time of the day.

If patient's body height/weight cannot be measured at screening because of the patient's physical condition, verbal height/weight is acceptable. Height/weight measurements shall be obtained as soon as the patient is physically able.

Body temperature and respiratory rate are measured at Screening, at 6, 12, 24 and 48 hours after the start of study drug infusion in the serelaxin arm, and daily through index hospitalization, at Day 5, at discharge, and then at Day 14. For the SOC patients, body temperature and respiratory rate are measured at Screening, at 6, 12, 24 and 48 hours after randomization, and daily through index hospitalization, at Day 5, at discharge, and then at Day 14, according to the scheduled visits. Patients discharged prior to Day 5 will be required to return to the hospital/clinic for Day 5 procedures.

Daily measurements may be made and recorded by trained study personnel as well as trained healthcare personnel as part of their routine clinical duties.

BP and pulse measurements are performed for all patients at the beginning of the screening period (after ICF signature) and at the end of the screening period (prior to randomization).

For serelaxin patients, BP and heart rate (HR) measurements are also performed before the immediate start of study drug administration (0 hours pre infusion start), throughout study drug infusion at 30 and 60 minutes, then every hour for the first 6 hours, and then every 3 hours, including night time hours. Post-infusion, BP and HR are to be measured every 3 hours until 12 hours following end of infusion, then every 6 hours for 48 hours and then every 24 hours through index hospitalization, at Day 5, at discharge, and then at Day 14. For patients randomized to the SOC group, BP and HR measurements should also be performed at 6, 12, 24, 48 hours post randomization, including night time hours, daily through index hospitalization, at Day 5, at discharge, and then at Day 14.

All measurements should be performed as close as possible to specified time point.

BP and HR are to be measured with the patient in the same position and with the same equipment using the same arm throughout study drug infusion. These measurements may be made and recorded by trained healthcare personnel as part of their routine clinical duties, as well as trained study personnel.

If at any time during dosing, the subject's systolic blood pressure decreases by > 40 mmHg from just before the study drug infusion baseline but is ≥ 100 mmHg in 2 consecutive measurements 15 minutes apart, serelaxin infusion rate should be decreased by 50% for the remainder of the 48 hour study drug administration. Serelaxin administration should be permanently discontinued at any time if in 2 consecutive measurements 15 minutes apart, systolic blood pressure reduces to < 100 mmHg.

Should the study drug dose be decreased or the study drug be discontinued prematurely due to blood pressure decrease, measurements should be taken every half hour through 2 hours

following the blood pressure decrease event, and then hourly through 5 hours after event onset. Upon completion of the 5 hour post event onset time point, heart rate and blood pressure measurements should be resumed as outlined above.

Physical examination findings

An overall physical examination is performed by the investigational staff at screening and includes the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and vascular and neurological examinations. An abbreviated physical examination is performed at 6, 12, 24 and 48 hours after start of study drug infusion in the serelaxin arm (from randomization for patients in the SOC arm), and daily through index hospitalization, at Day 5, at discharge, and then at Day 14, and includes the examination of general appearance and vital signs (SBP/DBP and pulse).

Following randomization, all physical examination should be performed at approximately the same time of day. Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to signing informed consent must be included in the Medical History part of the eCRF. Significant findings after signing the informed consent, up to and including Day 5, which meet the definition of an AE must be recorded on the Adverse Event section of the eCRF. Significant findings after signing the informed consent, up to and including Day 14, which meet the definition of an SAE must be recorded on the Serious Adverse Event section of the eCRF (Section 7.2 of the study protocol), and a completed signed Serious Adverse Event form must be faxed to the local Novartis Drug Safety and Epidemiology Department (DS&E) within 24 hours after awareness of the SAE.

Subjects discharged after 48 hours from the start of drug infusion for serelaxin arm/from randomization for SOC arm, but prior to Day 5, will be required to return for a physical examination as an outpatient at Days 5 and 14.

Clinical laboratory test results

All screening, baseline and post-baseline specimens [redacted] collected are analyzed by the local laboratory.

Clinical laboratory tests including hematology and chemistry are performed locally at screening, at 24 and 48 hours, at Day 5, at discharge, and then at Day 14 (in both arms). Urinalysis is conducted at baseline, 24 and 48 hours only and analyzed locally.

Clinical hematology evaluations include measurement of hemoglobin, hematocrit, white blood cell count, red blood cell count, differential cell count (monocytes, neutrophils, eosinophils, lymphocytes, basophils), and platelet count.

Serum chemistry evaluations include measurement of blood urea nitrogen (BUN) or urea, serum creatinine, total bilirubin, phosphate, ALT, AST, alkaline phosphatase, sodium, potassium, calcium, total cholesterol, triglycerides, LDL, HDL, glucose, uric acid, albumin, total

protein and eGFR. In addition, glycated hemoglobin (HBA1c) is measured at screening only, and eGFR is measured at screening, at 48 hours, at Day 5, and at discharge.

Urinalysis includes measurement of glucose, ketones, pH, protein and specific gravity.

Electrocardiogram (ECG)

12-Lead ECG evaluation is performed and interpreted locally at screening, at Day 5, and at discharge. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline.

Echocardiography

Echocardiography evaluation is not a mandatory requirement of the protocol; in case the evaluation is performed and the values obtained are available in the source documents, they need to be entered into eCRF. Most recent data up to the last 12 months can be entered.

Liver event

Details of liver events are collected throughout the study in dedicated eCRF sections, collecting an overview of the liver event and also medical history possibly contributing to liver dysfunction, history of alcohol use, history of drug abuse, imaging examination, pathology results, autoimmune details, viral serology, liver function test and acetaminophen/paracetamol administration.

Causes that lead to a re-hospitalization or emergency/urgent care >24 hours not resulting in admission

In case reason for re-hospitalization or emergency/urgent care >24 hours not resulting in admission is HF, renal impairment, cardiac (chest pain, ACS, MI), other cardiac, vascular, or non-cardiovascular, further details are collected in dedicated eCRF sections.

Survival and Death information

Details of vital status and death are collected throughout the study in the dedicated eCRF sections.

5. STATISTICAL METHODOLOGY

5.1. GENERAL METHODOLOGY

Data will be analysed according to the data analysis Section 9 of the study protocol.

All statistical tables, listings, figures and analyses will be produced using SAS® release 9.4 (64-bit) or later (SAS Institute Inc., Cary NC, USA).

The data from all countries and all sites will be pooled and summarized. Continuous data will be summarized by the mean, standard deviation (SD), median, first and third quartiles,

minimum and maximum. Categorical data will be presented by absolute and relative frequencies (n and %) or contingency tables.

All nominal time points will be used for analysis; actual assessment times will not be used to reclassify the time point at which a measure was taken. Time-to-event analyses will be based on actual dates (times) reported.

Subjects will be included in each efficacy analysis based on available assessments, after the data handling conventions have been applied. The prevalence approach (i.e., no imputation of missing data), if not differently indicated, will be applied.

Unless stated otherwise, two-sided p-values < 0.05 will be considered statistically significant. No formal interim efficacy analysis will be performed and therefore no statistical adjustment of alpha level will be required.

Visit, baseline and post baseline definitions

Screening phase: The screening phase is defined as the period prior to randomization. After obtaining written informed consent, the subject will be evaluated for eligibility to participate in the study.

Baseline definition for efficacy and safety measurements: Baseline date and time is defined as the date and time of initiation of study drug for the serelaxin group, or date and time of randomization for the SOC group. Of note, the randomization date and time will be used as the reference date and time for all time to event analysis.

Post-baseline phase for efficacy and safety measurements: The post-baseline phase begins at the date and time of initiation of study drug administration for the serelaxin group, or the date and time of randomization for the SOC group, and ends with the last study assessment/last follow-up or the death of subject. For subjects who did not receive study drug, the phase begins at the time of randomization.

Patient disposition and analysis population

A summary of participating countries and sites will be presented for the Screened Set, showing the total number of screened and randomized subjects. Sites which do not enrol any subject will be presented as well. The number of patients by region, country and treatment group will be presented for the FAS.

A complete description of patient disposition will be provided for SCR and FAS, overall and by treatment group, specifying the number of randomized patients, number of patients at each time point based on their latest available data, completed and discontinued patients at each study phase (screening, randomized treatment period, follow-up period), and the reason for the discontinuation. Relative frequencies will be also reported.

The number of patients in each of the analysis populations will be summarized and the reasons for excluding a patient from any particular population will be provided with the number of protocol deviations per each criterion. The number of mis-randomized patients will be provided as well. Percentages will be computed using the number of patients in the

randomized set as denominators. Moreover, any non randomized patient included in the Safety set will be reported.

The difference between treatment groups with respect to protocol deviations and reasons for drop-out will be examined. Descriptive statistics will be presented by treatment group for the length of follow-up (days), computed as the difference from the randomization date to the end of study date + 1 day (i.e., the last known vital status date, even through phone contact). Categorical summaries will also be presented for the number and percentage of subjects within predefined follow-up intervals as: >0-5 days; 6-14 days; 15-30 days; >30 days.

Patient demographics and other baseline characteristics

Demographic and baseline characteristics of patients, including derived variables, will be summarized in the FAS and Safety set, overall and by treatment group, with summary descriptive statistics. Continuous data will be summarized by means of standard summary statistics (i.e., number of observations, mean, standard deviation, median, first and third quartiles, minimum and maximum). Categorical data will be presented by absolute and relative frequencies (n and %); percentages will be computed considering non-missing information, if not differently specified.

Demographic and baseline characteristics will include sex, age (years), age category (<65 years, ≥65 years; <75 years, ≥75 years; 18-<65 years, ≥65-<85 years, ≥85 years), race, ethnicity, height (Centimeter), body weight (continuous and < 115 kg, ≥ 115 kg) at screening, body mass index (kg/m^2) at screening, body temperature (Celsius) at screening, respiratory rate (Breath/min) at screening, pulse (Beats/min) at start and end of screening and systolic and diastolic blood pressure (mmHg) at start and end of screening.

The above mentioned demographic and baseline characteristics will also be described by region (Western EU: Austria-Belgium-Denmark-Finland-France-Germany-Greece-Iceland-Italy-Portugal-Principality of Monaco-Spain-Switzerland-United Kingdom / Eastern EU: Bulgaria-Croatia-Czech Republic-Estonia-Hungary-Latvia-Lithuania-Poland-Romania-Russia-Serbia-Slovakia-Slovenia). If applicable, further possible country subgroups may be defined.

Patients' age will be computed in years elapsed from birth to the date of the informed consent signature. For patients with only year of birth reported (i.e., German sites), age entered by the investigator will be used without any computation.

Patients' height will be presented in centimetres; estimated and measured assessments will be analysed together.

Patients' body weight will be presented in kilograms; estimated and measured assessments will be analysed together.

Patients' body temperature will be presented in degrees Celsius.

Body mass index will be calculated as body weight (in kg) divided by the square of height (in m).

Background information will be summarized in the FAS and will include the following variables:

- Subject lifestyle history: highest level of education, subject's living arrangements and home health care arrangements.

- Prior history of heart failure (yes, no). Time from HF diagnosis to informed consent. It will be calculated in months elapsed between diagnosis date and informed consent date.

- Disease NYHA (New York Heart Association) class at approximately 1 month prior to admission for index heart failure event (class I - class IV).

- Primary heart failure etiology (ischemic, non-ischemic and details if non-ischemic). Percentages will be computed using the number of patients with a prior heart failure event as a denominator.

- Prior hospitalization due to heart failure (yes/no) and number of prior hospitalization due to heart failure in the last 12 months (0, 1, 2, 3, >3 and continuous). Moreover, the variable "Prior hospitalization due to heart failure in the last 12 months" will be derived as follows: "No" if there is no hospitalization in the past, or there is a hospitalization but the number of heart failure hospitalizations in the last 12 months is 0; "Yes" if the number of heart failure hospitalizations in the last 12 months is greater than 0.

- Ejection fraction (EF, %). Summary statistics will be presented for % values. Moreover, absolute and relative percentages of patients with EF levels <40% and ≥40%, and <50% and ≥50% will be presented. Methods used to determine EF levels will also be summarized.

- Presence of subject on heart transplant list (yes/no).

- Prior history of diabetes mellitus (yes/no, and if yes with details for control). Details of control will be presented with percentages computed using the number of patients with a prior history of diabetes mellitus as denominators.

- The medical history of protocol solicited events with "Occurrence" equal to "Yes" will be considered and will be presented by the code list reported in the eCRF. The description will be provided by status (ongoing or not), disease classification or severity as applicable. Percentages will be computed using the total number of patients in the analysis population as denominators.

- Alcohol history (amount of alcohol consumed in drinks per day).

- Drug abuse history (patient's usage status).

- Smoking history (patient's usage status).

- Medical history data not recorded as protocol solicited events or HF will be coded using the latest version of MedDRA, and will be presented by System Organ Class and Preferred Term, showing absolute and relative frequencies of patients having experienced each pathology. Description will be provided by status (ongoing or not). Percentages will be computed using the total number of patients in the analysis population as denominators.

- Summary statistics for eGFR at screening will be provided. Moreover, absolute and relative percentages of patients with eGFR levels, <25, ≥25 and <30, ≥30 and <60, ≥60 and <75, and ≥75 mL/min/1.73m^2 will be presented.

- Summary statistics for BNP, NT proBNP, serum cTnI and serum cTnT at screening will be provided. In addition to the conventional statistics, geometric mean and 95% CI will be reported.

- Summary statistics for clinical hematology, serum chemistry evaluations at screening and urinalysis evaluation at baseline will be provided.

- 12-lead ECGs overall interpretation at screening will be described (Normal/Clinically Insignificant Abnormality/Clinically Significant Abnormality). Moreover, heart rate (beats/min), mean PR duration (msec), mean QT duration (msec), corrected QT Fridericia interval and mean QRS duration (msec) will be described by means of standard summary statistics.

- Chest X-Ray at screening: procedure performed (yes/no) and overall interpretation will be summarized. Chest X-Ray is not considered as study related procedures and is performed according to local diagnostic practice.

- Echocardiography at screening: procedure performed (yes/no) and in which period, overall interpretation and LV Ejection Fraction (%). Echocardiography is not considered as study related procedures and is performed according to local diagnostic practice.

- EQ-5D-5L Health Questionnaire at baseline: summary statistics for each dimension score, including the subject overall self-rated health status measure (EQ VAS value), and index score, will be provided; further details are reported in section “5.2 Efficacy data”.
- Physician assessment of signs and symptoms of HF at baseline: absolute and relative frequencies of subjects reporting each sign/symptom will be provided.

In order to account for adequate interpretation of results, the homogeneity of patients’ distribution between treatment groups will be tested on demographic and anamnestic variables: gender, age, race, prior history of heart failure, NYHA disease classification, atrial

fibrillation in medical history ("Occurrence" is marked "Yes" on the "Medical History – Protocol Solicited Events" eCRF page), and atrial fibrillation at baseline ("Ongoing" is marked "Yes"). P-values will have a descriptive meaning and any warnings of heterogeneity will be evaluated considering the clinical relevance of the involved variables. The p-values will not be considered to define any formal basis for determining factors to be included in statistical models. If an imbalance of treatment groups with respect to some variables does occur, supplemental analyses with addition of these variables in model may be performed to assess the potential impact on efficacy as appropriate.

For continuous variables, homogeneity of data will be tested by means of t-test.

For categorical variables, Chi-square test will be used. Fisher's exact test will be used in cases where cell frequencies are less than 5.

Investigational treatment

Study treatment administration will be summarized for the FAS and the Safety set, for patients in the serelaxin arm only. Continuous variables (e.g., dose prescribed in mg, total volume administered in mL, rate of infusion in mL/hr, and duration of infusion in hours/days) will be summarized with standard summary statistics. Categorical variables (e.g., reason for dose change) will be summarized with the number and percentage of patients. Percentages will be computed using the number of patients with non-missing information as denominators, unless otherwise specified.

The analysis of study treatment will be performed for the FAS and Safety set, and will include the following variables:

- Time from presentation to randomization (hours) for both treatment groups. The date of presentation at screening is obtained from the "Index heart failure hospitalization" eCRF page. Time will be presented as elapsed hours and minutes and will be derived as difference + 1 minute. Analysis will be presented also by setting of presentation (Outpatient clinic or office/ Ambulance or Emergency Medical Service/ Emergency Department/ Intensive Care Unit/ Coronary or Cardiac Care Unit/ Cardiology ward/ General ward/ Other).

- Time from first IV loop diuretic administered for the treatment of the Index Heart Failure event to randomization (hours) for both treatment groups. The first IV loop diuretic administered for index heart failure is obtained from the start date and time of the IV loop diuretic recorded at screening on the "Index heart failure hospitalization" eCRF page. Time will be presented as elapsed hours and minutes and will be derived as difference + 1 minute.

- Study treatment administered (yes/no) for the serelaxin arm only: variable "Any dosage to report?" in the eCRF page "Dosage administration record" and reason why study treatment was not administered: variable "Subject Status" in the eCRF page "Treatment Completion" for patients with no dosage reported.

- Time from presentation to study treatment administration for patients with at least one reported dosage (hours) in the serelaxin arm only. Date of presentation recorded is the earliest of (1) time of presentation either at the ER, ICU/CCU or ward (excludes EMS or other pre-hospital care); or (2) time of first IV loop diuretic prior to arrival at the hospital (this includes in the clinic, ambulance, or any other setting) for the treatment of the current acute heart failure episode. The date of presentation at screening is obtained from the "Index heart failure hospitalization" eCRF page. The date of study treatment administration for patients with at least one reported dosage is obtained from the start date and time of study treatment with a non-missing prescribed dose recorded on the "Dosage administration record" eCRF page. Time will be presented as elapsed hours and minutes and will be derived as difference + 1 minute. Analysis will be presented also by setting of presentation (Outpatient clinic or office/ Ambulance or Emergency Medical Service/ Emergency Department/ Intensive Care Unit/ Coronary or Cardiac Care Unit/ Cardiology ward/ General ward/ Other).

- Time from randomization to study treatment administration (hours) for patients in the serelaxin arm only. The date of study treatment administration is obtained from the start date and time of study treatment with a non-missing prescribed dose recorded on the "Dosage administration record" eCRF page. Time will be presented as elapsed hours and minutes and will be derived as difference + 1 minute.

- Total volume of study treatment administered (mL) for patients in the serelaxin arm only is estimated from the duration of infusion in hours and the corresponding rate of infusion in mL/hr. It will be computed as the sum of the reported total volumes of study treatment throughout the study.

- Duration of study treatment administration (hours) for patients in the serelaxin arm only. It will be presented as elapsed hours and minutes +1 minute from the start to the end of infusion; any temporary treatment interruptions will not be detracted. Number of days study treatment infused: the following discrete categories will be computed and described, <1 day (i.e., <1440 minutes), between 1 and 2 days (i.e., >=1440 and <=2880 minutes) and >2 days (i.e., >2880 minutes). The continuous variable duration of study treatment infusion in days and in hours will be summarized as well.

- Any dose reduction (yes/no) and reason for dose reduction for patients in the serelaxin arm only. A dose reduction is defined as a rate of infusion lower than the rate of infusion reported in the previous infusion record. Reason for dose reduction will be summarized and percentages will be computed on total number of dose reduction. Number and percentages of patients who reported any dose reduction by reason for dose reduction will be provided.

- Number of patients for whom study medication dose was discontinued prematurely, and the reason for discontinuation for patients in the serelaxin arm only. Patients who

discontinued prematurely the study drug are defined as patients with at least one dose infusion and "Subject Status" on the eCRF page "Treatment Completion" different from 'Completed'. The "Subject Status" will be summarized as well.

- A listing of patients with actual treatment received different from randomized treatment will be provided for the Safety set only for both arms.

Logistic regression models will be fitted considering demographics and anamnestic factors in order to identify main predictors for study drug discontinuation. Odds ratio and 95% confidence intervals will be provided.

Univariate regression models will be fitted considering as factors the following variables: age, gender, BMI at screening. Moreover, a multivariate regression model will be fitted considering all the factors above mentioned and selected with a stepwise method.

Patients who discontinued prematurely the study drug are defined as subjects with at least one dose infusion recorded on the "Dosage administration record" eCRF page and "Subject Status" on the eCRF page "Treatment Completion" different from 'Completed'.

Concomitant treatments

Concomitant medications are collected in dedicated eCRF sections at screening, baseline, 24h, 48h, Day 3, Day 4, Day 5, Day 14, Day 30 and discharge visit; in general, medications taken within the screening period are collected at Screening; medications taken since the initial presentation of the Index Heart Failure event are reported at baseline; medications taken within the 24 hours preceding the visit are entered in eCRF at each post baseline assessment.

Concomitant medications usage will be described by treatment group according to the following details. Medications will be coded using the WHO NOVDD_14_3 dictionary and subsequent versions. As a patient may have taken more than one medication, the total number of medications could be greater than the total number of patients. Continuous variables will be summarized with standard summary statistics, categorical variables with the number and percentage of patients. Percentages will be computed using patients included in the analysis population as denominators.

All medications reported in the eCRF pages corresponding to the day of discharge will be considered as administered during the index hospitalization.

Concomitant treatment administration details will be summarized by treatment group for the FAS and the Safety set.

The analysis will include the following variables:

- Any IV nitrates at the time of randomization (yes/no). A complete description will be provided also by medication, with number and percentage of patients taking at least one dose of medication (obtained from start date and time and non-missing dose recorded at screening on the "Index heart failure hospitalization" eCRF page).

- Any IV loop diuretic medication taken since the initial presentation of heart failure (recorded as "Any medication to report?" in the "IV loop diuretic medication for heart failure" dedicated eCRF page from baseline visit) (yes/no). A complete description will be provided also by Preferred Term for other medication names not listed in the eCRF, with number and percentage of patients taking at least one dose of medication. Moreover, the total dose of IV loop diuretic administered during the index hospitalization (at most for 5 days of hospitalization) will be described. Doses will be converted to Furosemide equivalents for the analysis (Furosemide 40 mg is equivalent to Torasemide/Torsemide 20 mg, or Bumetanide 2 mg, or Etacrynic acid/Ethacrynic acid 50 mg, see Table 5.1-2 below for the conversion factors). The total dose of IV loop diuretic administered during the index hospitalization will be compared between treatment groups using a t-test. For subjects who die before Day 5, the minimum of 2 times of the last recorded dose and 160 mg will be assumed for every day from the date of death up to and including Day 5. Data will be presented overall and by day from randomization. Data after the index hospitalization will be presented separately.

Table 5.1-2: Conversion factor for diuretic medications

Original Unit	Preferred Unit	Multiplication Factor
Furosemide (mg)	Furosemide (mg)	1
Torasemide (mg)	Furosemide (mg)	2
Bumetanide (mg)	Furosemide (mg)	20
Etacrynic acid (mg)	Furosemide (mg)	0.8

- Any oral (PO) loop diuretic medication taken since the initial presentation (recorded with "PO loop diuretics" ticked on the "Other non-IV medications" dedicated eCRF page from baseline visit) (yes/no). A complete description will be provided also by preferred term for the other name of medication, with number and percentage of patients taking at least one dose of medication. Moreover, the total dose of oral loop diuretic administered during the index hospitalization (at most for 5 days of hospitalization) will be described. Doses will be converted to Furosemide equivalents for the analysis (see Table 5.1-2). The total dose of PO loop diuretic administered during the index hospitalization will be compared between treatment groups using a t-test. For subjects who die before Day 5, the minimum of 2 times of the last recorded dose and 160 mg will be assumed for every day from the date of death up to and including Day 5. Data will be presented overall and by day from randomization. Data after the index hospitalization will be presented separately.

- All non-IV medications taken since the initial presentation (recorded on the "Other non-IV medications" dedicated eCRF page from baseline visit), excluding Per Oral (PO) loop diuretics, will be summarized by medication classification and name of medication, presenting number and percentage of patients taking at least one dose of medication. Data will be presented overall during index hospitalization and by day from randomization. Data after the index hospitalization will be presented separately.

- All IV medications other than loop diuretics taken since the initial presentation (recorded in the dedicated eCRF page from baseline visit) and by day from randomization will be summarized by medication classification and name of medication, presenting number and percentage of patients taking at least one dose of medication. Data will be presented overall during index hospitalization. Data after the index hospitalization will be presented separately.

- All other non-IV prior medication taken 30 days before screening (recorded in the "Other non-IV prior medication" dedicated eCRF page at screening visit) will be summarized by name of medication, presenting number and percentage of patients taking at least one dose of medication.

- All procedures/tests/treatments performed overall during the index hospitalization (recorded in the "Index heart failure hospitalization – procedures/tests/treatments performed" dedicated eCRF page from Day 5) will be summarized presenting the number and percentage of patients reporting the procedure, test or treatment. Tabulation will follow the code list reported in the eCRF.

5.2. EFFICACY DATA

The primary analysis and the analyses of all secondary and exploratory efficacy variables will be based on the FAS. In addition to the primary analysis, the primary efficacy variable will also be analysed using the same primary analysis model on the PP set as supportive information.

Primary efficacy parameter

Worsening Heart Failure/all cause death through Day 5

The primary efficacy variable of the study is the time to in-hospital Worsening of Heart Failure (WHF) requiring rescue therapy or all cause death through Day 5 post randomization.

In-hospital worsening of heart failure (WHF) through Day 5 post randomization includes worsening signs and/or symptoms of heart failure that require an intensification of intravenous therapy for heart failure or mechanical ventilation, renal or circulatory support. Such treatment can include the institution or up-titration of IV furosemide, IV nitrates or any other IV medication for heart failure, or institution of mechanical support such as assisted (invasive or non-invasive) ventilation, ultrafiltration, hemodialysis, intra-aortic balloon pump or ventricular assist device, etc. This endpoint also includes patients who die in this 5-day period of any cause before experiencing episode(s) of WHF.

Time to in-hospital WHF/all cause death through Day 5 post randomization will be analysed using survival analysis.

The time to in-hospital WHF/all cause death will be computed as the number of hours from randomization to the earlier of the onset of in-hospital WHF or death plus 1 minute. The onset of in-hospital worsening heart failure through Day 5 will be the start date/time of event

reported at the first assessment point at which the investigator reported worsening heart failure; if death occurred, date and time are reported in the dedicated eCRF section. Subjects without an event will be censored at the earlier of the last post-baseline assessment date or 120 hours after randomization. Subjects without any information after baseline (i.e., randomization) will be considered censored at 1 minute.

In case of missing time of in-hospital WHF or death then 00:00 will be imputed.

Only adjudicated endpoints will be counted in the primary analysis. The "adjudicated endpoint" refers to an endpoint and date of the endpoint that has been confirmed by an independent adjudication committee who has no access to the treatment code. According to the information from the endpoint adjudication committee, the following rules will be applied to determine if an event reported in eCRF should be considered valid for the analysis or not:

Table 5.2-1: Rule for inclusion of events into the analysis

	Included in the analysis
WHF/death reported in the dedicated page of the eCRF and confirmed by adjudication committee	YES
WHF/death reported in the dedicated page of the eCRF and NOT confirmed by adjudication committee	NO

If more than one in-hospital WHF occurred, the first one will be used as the event. Censoring and time will be defined according to the following rule:

Table 5.2-2: Censoring and time rules

	Status	Time
At least one in hospital WHF and/or death occurred and:		
Difference between date and time of first occurrence of WHF/death and date and time of randomization +1 minute >120 hours	Censored	120h
Difference between date and time of first occurrence of WHF/death and date and time of randomization +1 minute ≤120 hours	Event	Calculated difference
No in hospital WHF and death occurred and:		
Difference between date and time of last assessment* and date and time of randomization +1 minute >120 hours	Censored	120h
Difference between date and time of last assessment* and date and time of randomization +1 minute ≤120 hours	Censored	Calculated difference

* Last assessment is the date and time of last available post-baseline physician assessment of in-hospital WHF

In case a patient is lost to follow-up, events occurring prior to the time of lost to follow-up will be counted. If no event occurred, then the patient will be censored at the time of last post-baseline in-hospital WHF assessment available.

The primary statistical hypothesis is:

H_0: $\lambda_2/\lambda_1 \geq 1$, i.e., the rate of primary event of in-hospital WHF or all cause death is greater or equal in the serelaxin group relative to the standard of care group versus the one-sided alternative H_A: $\lambda_2/\lambda_1 < 1$, i.e., the rate of in-hospital WHF or all cause death is smaller in the serelaxin group relative to the standard of care group, where λ_1 and λ_2 are the hazard rates for in-hospital WHF or all cause death in the standard of care group and serelaxin group, respectively. The ratio λ_2/λ_1 is the hazard ratio of serelaxin to standard of care.

The hypothesis will be tested based on the FAS with a Gehan's generalized Wilcoxon test at a significance level of 0.025 (one-sided).

The Kaplan-Meier estimates of the survival functions for each treatment group will be plotted and Kaplan-Meier estimates for selected time points with 95% confidence intervals will be tabulated.

The hazard ratio (relative risk) and its associated two-sided 95% confidence interval will be estimated based on a Cox proportional hazards model with treatment assignment as a factor.

[redacted]

In addition, a description of all in-hospital WHF that occurred through Day 5 will be provided: absolute frequencies and proportions of patients with in-hospital WHF at each assessment time point will be presented overall and by concomitant medication (IV therapy with vasoactives, IV therapy with loop diuretics, oral therapy with loop diuretics, IV therapy with inotropes vasoactives) given (new, restarted or increased dose of medication), and/or by the need of mechanical/surgical intervention (yes/no) for the in-hospital WHF.

In addition to the primary analysis, the primary efficacy variable will also be analysed using the same primary analysis model on the PP set as supportive information.

Subgroup (age [65 and 75 cut off], gender, race [Caucasian and other race], region [Western Europe and Eastern Europe], ejection fractions [40% and 50% cut off], prior history of HF [naïve vs. prior history of HF]) analyses will be performed for the primary endpoint.

A Cox proportional hazards model will be fitted considering treatment as a factor and covariates the above mentioned subgroup variables. The hazard ratio (relative risk) and its associated two-sided 95% confidence interval will be estimated for treatment and factors/covariates.

An additional supportive analysis of the primary efficacy variable will be performed using all WHF/all cause deaths through Day 5 post randomisation as reported by the investigators, regardless of confirmation from the endpoint adjudication committee.

The time to WHF/all cause deaths through Day 5 post randomisation will be as described for the primary analysis.

The Kaplan-Meier estimates of the survival functions for each treatment group will be plotted. Kaplan-Meier estimates at selected time points and their 95% confidence intervals will be provided.

[redacted]

Handling of missing values/censoring/discontinuations

In the analysis of time to in-hospital WHF/all-cause death through Day 5, patients without any event will be censored at the earlier of the last post-baseline physician assessment of in-hospital WHF or 120 hours post randomization.

Subjects without any information after baseline (i.e., randomization) will be considered censored at 1 minute.

In case of missing time of in-hospital WHF or death then 00:00 will be imputed.

Secondary efficacy parameters

The additional efficacy endpoints will be analysed in the FAS. Standard descriptive statistics will be presented for each treatment group at each time point that the endpoint was measured. Two-sided p-values <0.05 will be considered statistically significant; no adjustment for multiple comparisons will be adopted.

Time to in-hospital WHF/All cause death/readmission for heart failure through Day 14 post randomization

Time to in-hospital WHF/all cause death/readmission for heart failure through Day 14 post randomization will be analyzed using survival analysis.

The time to in-hospital WHF/all cause death/readmission will be computed as the number of hours from randomization to the earlier of the onset of in-hospital WHF or death or readmission for heart failure plus 1 minute. The onset of in-hospital WHF through Day 14 will be the start date/time of event reported at the first assessment point at which the investigator reported worsening heart failure (either during the initial hospitalization or re-hospitalization for heart failure); if death occurred, date and time are reported in the dedicated eCRF section “Death – (Endpoint to be adjudicated)”; the date and time of admission of first re-hospitalization with Primary reason for Hospitalization equal to “Heart Failure” will be considered as the readmission moment (as reported in the dedicated eCRF section “Rehospitalization Information (Endpoint not to be adjudicated)”. Subjects without an event will be censored at the earlier of the last post-baseline assessment or 336 hours after randomization. Subjects without any information after baseline (i.e., randomization) will be considered censored at 1 minute.

In case of missing time of in-hospital WHF or death or rehospitalisation for heart failure then 00:00 will be imputed.

According to the information from the endpoint adjudication committee, the following rules will be applied to determine if an endpoint reported in eCRF should be considered valid for the analysis or not:

Table 5.2-3: Rule for inclusion of events into the analysis

	Included in the analysis
WHF/death occurred within Day 5, reported in the dedicated page of the eCRF and confirmed by adjudication committee	YES
WHF/death occurred within Day 5, reported in the dedicated page of the eCRF and NOT confirmed by adjudication committee	NO
WHF/death occurred after Day 5 through Day 14 and reported in the dedicated page of the eCRF	YES
Readmission for heart failure reported in the dedicated page of the eCRF	YES

Censoring and time will be defined according to the following rule:

Table 5.2-4: Censoring and time rules

	Status	Time
At least one in hospital WHF/death/readmission for HF occurred and:		
Difference between date and time of first occurrence of WHF/death/readmission for HF and date and time of randomization +1 minute >336 hours	Censored	336h
Difference between date and time of first occurrence of WHF/death/readmission for HF and date and time of randomization +1 minute ≤336 hours	Event	Calculated difference
No in hospital WHF/death/readmission for HF occurred and:		
Difference between date and time of last assessment* and date and time of randomization +1 minute >336 hours	Censored	336h
Difference between date and time of last assessment* and date and time of randomization +1 minute ≤336 hours	Censored	Calculated difference

* Last assessment is the date and time of last available post-baseline physician assessment of in-hospital WHF

In case a patient is lost to follow-up, only the data until the last post-baseline in-hospital WHF assessment available will be considered in the analysis.

Treatment groups will be compared with a Gehan's generalized Wilcoxon test. The Kaplan-Meier estimates of the survival functions for each treatment group will be plotted. The Kaplan-

Meier estimates of the cumulative event rate will also be presented in tables by treatment group for each day and also by time interval (>0-5 days, >5-14 days).

Absolute frequencies and proportions of patients with event (as defined in the time to event analysis), overall (in-hospital WHF/all cause death/readmission) and by type of event (in-hospital WHF; all cause death; readmission), through Day 14 in each treatment group will also be provided (percentages based on population of analysis).

In addition, a description of all in-hospital WHF that occurred through Day 14 will be provided: absolute frequencies and proportions of patients with in-hospital WHF at each assessment time point will be presented overall and by the concomitant medication given (new, restarted or increased dose of medication), and/or by the need of mechanical/surgical intervention (yes/no) for the in-hospital WHF.

A summary of number and percentage of patients with or without WHF events through Day 5 (recorded on "Clinical worsening of heart failure" eCRF page for adjudicated events), and from Day 6 through Day 14 (recorded on "Heart failure details" eCRF page for events not to be adjudicated), will be provided by treatment.

Persistent signs or symptoms of HF/ non-improvement

Absolute frequencies and proportions of patients with persistent symptoms or signs of HF / not showing an improvement at any visit vs. baseline (persisting need of IV therapy for HF) in each treatment group will be provided, and also at each assessment time point (24 hours, 48 hours, Day 3, Day 4) through Day 5 and at discharge, together with standard errors, asymptotic (Wald) and exact (Clopper-Pearson) confidence limits. The rates in the two groups will be compared by means of Chi square test at each time point. In case of cell frequencies less than 5, Fisher's Exact test will be used.

Patients with persistent symptoms or signs of HF / not showing an improvement versus baseline conditions at each assessment time point are those patients who take any IV therapy for HF at the assessment time point as reported in the eCRF sections "IV Loop Diuretic Medication for Heart Failure" and "IV Medications Other than Loop Diuretics".

Improvement in signs or symptoms of HF

A time-to-event analysis through Day 14 will be performed. Hazard ratios of being a responder for each of the signs and symptoms variables (response is defined as ≥1 point improvement from baseline) will be estimated using a Cox regression model with treatment as a factor.

Treatment groups will be compared with a Gehan's generalized Wilcoxon test. The Kaplan-Meier estimates of the cumulative event rate will also be presented by treatment group.

One or more point improvement will be defined as a reduction from baseline of at least one point in the specific sign/symptom according to the score defined in the table below.

Table 5.2-5: Scores for the definition of improvement

	Categorical value	Numerical value
Dyspnea on exertion	None	0
	Mild	1
	Moderate	2
	Severe (including dyspnea at rest)	3
Orthopnea	None	0
	1 pillow (10cm)	1
	2 pillows (20cm)	2
	>30 degrees	3
Edema	0	0
	1+	1
	2+	2
	3+	3
Rales	No rales	0
	Rales <1/3	1
	Rales 1/3-2/3	2
	Rales >2/3	3
Jugular venous pulse (JVP)	<6cm	0
	6-10cm	1
	>10cm	2
Body weight increase	No	0
	Yes	1

The scores will be presented as both categorical and continuous (i.e., numerical values in Table 5.2-5) statistics. Change from baseline will be computed as the baseline value subtracted from the post baseline values. Cross tabulation of categorical values at baseline and at each assessment time point will be presented by treatment group.

Each sign or symptom of HF, collected in "Physician Assessment of Signs and Symptoms of Heart Failure" eCRF page, will be analysed separately. The event is defined as ≥1 point improvement from baseline. The time to being a responder will be computed as the number of hours from randomization to the date and time of the first assessment at which a ≥1 point improvement from baseline is detected plus 1 minute. Subjects without an event will be censored at the earlier of the last post-baseline assessment of signs and symptoms of HF or 336 hours (i.e., 14 days) after randomization. Subjects without any information after baseline (i.e., randomization) will be considered censored at 1 minute. In case of missing time of assessment of signs and symptoms of heart failure then 00:00 will be imputed. The analysis will be performed excluding subjects with the following signs and symptoms at baseline: 'None' for Dyspnea on exertion and Orthopnea; '0' for Edema; 'No rales' for Rales; '<6 cm' or 'Not evaluable' for Jugular venous pulse, 'No' for Body weight increase.

Table 5.2-6: Censoring and time rules

	Status	Time
At least one (≥1) point improvement occurred and:		
Difference between date and time of first occurrence improvement (i.e., date and time of physician assessment where improvement was assessed) and date and time of randomization +1 minute >336 hours	Censored	336h
Difference between date and time of first occurrence improvement (i.e., date and time of physician assessment where improvement was assessed) and date and time of randomization +1 minute ≤336 hours	Event	Calculated difference
No improvement occurred and		
Difference between date and time of last available physician assessment and date and time of randomization +1 minute >336 hours	Censored	336h
Difference between date and time of last available physician assessment and date and time of randomization +1 minute ≤336 hours	Censored	Calculated difference

Moreover, summary statistics for data about physician assessment of signs and symptoms of HF will be provided at each assessment time point by treatment group. Absolute and relative frequencies of patients reporting each sign/symptom will be provided. Percentages will be computed considering patients with non-missing information at each assessment time point and by each type of sign and symptom.

Renal deterioration

Renal deterioration will be assessed as the proportion of patients with an increase of ≥0.3 mg/dL from screening in serum creatinine levels. Absolute frequencies and proportions of patients with renal deterioration at each assessment time point in each treatment group will be provided, together with standard errors, asymptotic (Wald) and exact (Clopper-Pearson) confidence limits. Rate of renal deterioration in the two groups will be compared by means of Chi square test at each assessment time point. In case of cell frequencies less than 5, Fisher's Exact test will be used.

Index length of hospital stay

Index length of hospital stay (in hours) will be defined as the index hospitalization discharge date and time (obtained from the "Index hospitalization summary" eCRF page) minus the index hospitalization admission date and time plus 1 minute (obtained from the "hospitalization" eCRF page); it will be presented as elapsed hours.

Subjects still in the hospital at Day 30 will be censored at Day 30. Subjects who die during the initial hospitalization will be assigned the maximum length of stay (including those censored at Day 30) plus 24 hours.

Treatment groups will be compared using a Wilcoxon rank-sum test. Descriptive statistics by treatment group will be presented. Analysis will be done overall and by location for patients presented to Outpatient clinic or office / Ambulance or Emergency Medical Service / Emergency Department / Intensive Care Unit / Coronary or Cardiac Care Unit / Cardiology Ward / General Ward / Other, as recorded on the "Index heart failure hospitalization" eCRF page.

Estimated duration (days) of stay in acute care unit (Coronary or cardiac critical care unit / General intensive care unit / Step down unit or telemetry unit / Cardiology department or cardiac ward / General ward), as recorded on the "Index hospitalization summary" eCRF page, will be summarized by treatment group.

Death through Day 30

The time (in days) from randomization to the event plus 1 day will be used for analysis. If death occurred, date is reported in the dedicated eCRF sections "Death – (Endpoint to be adjudicated)" or "Death – (NOT to be adjudicated)". Subjects without an event will be censored at the earlier of the last contact date (Last known date patient alive in "Survival Information" section) or Day 30. Subjects without any information after baseline will be considered censored at 1 day.

Table 5.2-7: Censoring and time rules

	Status	Time
Death occurred:		
Difference between date of death and date of randomization +1 day >30 days	Censored	30 days
Difference between date of death and date of randomization +1 day ≤30 days	Event	Calculated difference
No death occurred:		
Difference between date of last survival status* and date of randomization +1 day >30 days	Censored	30 days
Difference between date of last survival status* and date of randomization+1 day ≤30 days	Censored	Calculated difference

* Last survival status is the last known date patient was alive

Treatment groups will be compared using a generalized Wilcoxon test. The Kaplan-Meier estimates of the survival functions for each treatment group will be plotted and summarized.

Re-hospitalization post-discharge

Patients not discharged from the index hospitalization will not be included in the summary of number of re-hospitalizations.

The number of re-hospitalizations per patient by treatment group will be described. Treatment groups will be compared using a Wilcoxon rank-sum test.

The number of patients with re-hospitalization will be summarized. Categories of patients' number of re-hospitalizations will be 0, 1, 2, >2, and will be compared between treatment groups with a Chi-Square test. In case of cell frequencies less than 5, Fisher's Exact test will be used. Cochran-Armitage Test for trend will also be performed.

Patients not discharged from the index hospitalization will be included in the analysis of time to first re-hospitalization.

Time to first re-hospitalization (in days) will be defined as the first re-hospitalization date (Date of admission in "Rehospitalization Information") minus the randomization date plus 1 day. Subjects still in hospital at Day 30 will be censored at Day 30, calculated as randomization date + 30 days. Subjects who die after index hospitalization discharge or when not hospitalized will be assigned the date of death as their time to re-hospitalization. Similarly, subjects who died during index hospitalization without being discharged will have their date of death as their time to re-hospitalization.

Table 5.2-8: Censoring and time rules

	Status	Time
Patient not discharged from index hospitalization at Day 30	Censored	30 days
Patient not discharged but who died during index hospitalization:		
Difference between date of death and date of randomization +1 day >30 days	Censored	30 days
Difference between date of death and date of randomization +1 day ≤30 days	Event	Calculated difference
Patient discharged from index hospitalization and with at least one re-hospitalization:		
Difference between date of first re-hospitalization and date of randomization +1 day >30 days	Censored	30 days
Difference between date of first re-hospitalization and date of randomization +1 day ≤30 days	Event	Calculated difference
Patient discharged from index hospitalization but without re-hospitalization:		
Difference between date of last visit* and date of randomization +1 day >30 days	Censored	30 days
Difference between date of last visit* and date of randomization +1 day ≤30 days	Censored	Calculated difference
Patient discharged from index hospitalization but who died without re-hospitalization:		
Difference between date of death and date of randomization +1 day >30 days	Censored	30 days
Difference between date of death and date of randomization +1 day ≤30 days	Event	Calculated difference

* Last visit includes date of last visit (if subject is alive at the study termination)

Treatment groups will be compared using a Gehan's generalized Wilcoxon test. The Kaplan-Meier estimates for each treatment group will be plotted. Descriptive statistics by treatment group will be presented.

Re-hospitalisation characteristics, such as type of re-hospitalisation (urgent/emergency or elective) and reason (both primary and detailed), will be described presenting absolute frequencies and percentages calculated on the total of re-hospitalizations occurred with non-missing information. Estimated duration (days) for specific acute care units (recorded on the "Rehospitalization information" eCRF page) will be summarized by treatment group providing number of observations, mean, standard deviation, median, first and third quartiles, minimum and maximum. Absolute and relative frequencies of patients presenting at least one re-hospitalisation by type (urgent or elective) and by primary reason will be provided; percentages will be computed using the total number of patients discharged from index hospitalization as denominators.

All procedures/tests/treatments performed (recorded on the "Rehospitalization – procedures/tests/treatments performed" eCRF page) will be summarized presenting number and percentage of subjects reporting the procedure/test/treatment; the data will be summarized overall and percentages will be calculated using subjects with at least one re-hospitalization as denominators. Tabulation will follow the code list reported in the eCRF.

Resource utilization

Summary statistics on data about healthcare resource utilization collected throughout the index hospitalization, at discharge and at Day 5, and then at Day 14 post randomization, and through phone contact at Day 30 post randomization will be provided by treatment group.

Index hospitalization length of stay (days) for specific acute care units will be summarized by treatment group providing number of observations, mean, standard deviation, median, first and third quartiles, minimum and maximum. Total length of stay for each specific acute care unit will be calculated by summing the estimated duration (days) at each assessment point.

Absolute frequencies and percentages of subjects discharged and location of discharge (home / long term care facility) will be provided by treatment group.

In addition, description of emergency/urgent care > 24 hours not resulting in admission will be provided by treatment. Number of subjects with 0, 1, 2, >2 events will be summarized and compared between treatment groups with a Chi-Square test. In case of cell frequencies less than 5, Fisher's Exact test will be used. Cochran-Armitage Test for trend will also be performed.

Reason for emergency/urgent care visit > 24 hours not resulting in admission (both primary and detailed) will be described presenting absolute frequencies and percentages calculated on the total of emergency/urgent care visits with non-missing information. Absolute and relative frequencies of patients presenting at least one emergency/urgent care visit by primary reason will be provided; percentages will be computed using the total number of patients discharged from index hospitalization as denominators.

All tests performed at the emergency/urgent care visit will be summarized presenting number and percentage of subjects reporting the test; the data will be summarized overall and percentages will be calculated using subjects with at least one emergency/urgent care visit as denominators. Tabulation will follow the code list reported in the eCRF.

Health-related Quality of Life

Health-related quality of life assessments, by means of the EuroQoL EQ-5D-5L questionnaire, will be used to derive pre-specified quality of life scores according to the EuroQoL EQ-5D-5L questionnaire manual.

The EQ-5D-5L consists of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression); each dimension has 5 levels of answer: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patient is asked to indicate his/her health state for each of the 5 dimensions; the decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the subject's health state. It should be noted that the numerals 1-5 have no arithmetic properties and should not be used as a cardinal score. A total of 3,125 possible health states are defined; each state is referred to in terms of a 5-digit code.

Each dimension will be summarized at baseline and at each assessment time point by treatment group providing absolute and relative frequencies of each level answer (percentages will be calculated on non-missing data for each dimension). Results will be provided also for subgroup variables such as age (i.e., <65 vs. ≥65 years), gender and region (i.e., Eastern Europe vs. Western Europe).

EQ-5D-5L levels will be also dichotomised into 'no problems' (i.e., level 1) and 'problems' (i.e., levels 2 to 5), therefore changing the profile into frequencies of reported problems. Dichotomised variable in the two groups will be compared by means of Chi square test at each assessment time point. In case of cell frequencies less than 5, Fisher's Exact test will be used.

Each dimension will be summarized at Day 2, Day 5 and Day 14 assessment time points post randomization by treatment group, also providing absolute and relative frequencies of each level answer (percentages will be calculated on non-missing data for each dimension) by baseline level answer and by hospitalization status (hospitalized/not hospitalized) at study visit.

Summary statistics (number of observations, mean, standard deviation, median, first and third quartiles, minimum and maximum) of raw data and change (absolute and %) from baseline will be provided at each assessment time point for the subject's overall self-rated health status measure (EQ VAS values) by treatment group and by hospitalization status (hospitalized/not hospitalized) at study visit. The value of 100 is the best health the subject can imagine; 0 is the worst health the subject can imagine. Treatment groups will be compared for changes (absolute) from baseline using t-tests.

Summary statistics of raw data and change (absolute and %) from baseline will also be provided at each assessment time point for subgroup variables such as age (i.e., <65 vs. ≥65 years), gender, region (i.e., Eastern Europe vs. Western Europe), and occurrence of at least one WHF through Day 14.

If data do not respect normality assumption, a Wilcoxon rank sum test will be applied.

EQ-5D-5L health states will be converted into a single index value using UK as the reference country for all countries. Studies that derive values sets and procedure for the index computation are under development in a number of countries; the most updated SAS code from the EQ Executive Office will be applied (i.e. reference set for UK updated on January 2016 obtained from "*Devlin, N., Shah, K., Feng, Y., Mulhern, B. and van Hout, B., 2016. Valuing Health-Related Quality of Life: An EQ-5D-5L Value Set for England. OHE Research Paper 16/01. London: Office of Health Economics*"). Summary statistics will be provided for the index value at each visit by treatment group.

To compare treatment groups in quality of life change from baseline (i.e., randomization), a mixed model for repeated measures will be fitted to overall health index score absolute changes from baseline (score at time of assessment - score at baseline), and considering treatment, visit and treatment by visit as factors, and value at baseline as covariate.

If data do not respect normality assumption, a rank transformation will be applied.

The questionnaire/scale completion status will be summarised descriptively by treatment group at each visit.

5.3. SAFETY DATA

All the safety analyses will be done on the Safety set.

Adverse events

The incidence of Adverse Events (AEs) recorded through Day 5 and Serious Adverse Events (SAEs) recorded through Day 14 will be presented for the Safety set. Treatment emergent AEs/SAEs will be considered as those AEs/SAEs with an onset date and time after treatment initiation for the serelaxin group. For the Standard of Care Only group, date and time of randomization will be considered as treatment initiation. In case of missing time of onset of the event, only the onset date will be used for the evaluation of the incidence of the AE. Adverse events with an onset between informed consent and treatment initiation will be listed separately.

Tables reporting general summary of AEs will be produced by treatment group specifying the number of total events and absolute and relative frequency of patients with AEs. As a patient may have more than one AE, the total number of AEs could be greater than the total number of patients. Further summaries by treatment group will be produced for non-serious AE and serious AE by time period, e.g., through Day 5 and through Day 14.

Absolute and relative frequency of patients with drug-related AEs, severe AEs, SAEs, AEs with an outcome of death, AEs leading to permanent discontinuation of treatment, AEs indicative of safety risk and events of interest (please refer to the section below for the definition of safety risk events and events of interest) will also be reported for treatment emergent AEs. The number of distinct adverse events by low level term will be provided. Drug-related AEs will be the AEs with relationship to study treatment equal to "Yes", "Yes, investigational treatment", "Yes, other study treatment (not-investigational)", "Yes, both and/or indistinguishable"; if the

relationship to study drug is unknown or missing, the AE will be considered to be drug-related as well. eCRF severe events will be considered as severe events in the analysis. These summaries will be repeated for treatment emergent SAEs.

Treatment emergent AEs will be tabulated by System Organ Class (SOC) and Preferred Term (sorted in alphabetical order within each SOC) using the latest MedDRA dictionary, and by System Organ Class, Preferred Term and severity. Absolute and relative frequency of patients who have experienced each type of event will be presented; if the same patient reported more than one occurrence of the same AE with different intensity, the worst reported severity grade for each event for the patient will be used for the analysis. The most frequent treatment emergent AEs will also be tabulated by Preferred Term sorted by descending frequency for AEs with an incidence rate of at least 5% in the serelaxin group.

In addition, treatment emergent adverse events associated with

- worsening heart failure (WHF)/all cause death through Day 5
- confirmed systolic blood pressure decrease event (CBPDE)

will be summarized by system organ class and preferred term. These AEs are determined by taking the answer “Yes” to the questions “Does AE meet the definition of Endpoint?” and “Does AE meet the definition of Systolic Blood Pressure Decrease Event?”, respectively.

Treatment emergent SAEs will be summarized similarly. Treatment emergent SAEs will be summarized by time period of onset, i.e., through Day 5 and through Day 14. Treatment emergent SAEs are defined as those which start after treatment start for serelaxin group, or after randomization for Standard of Care group.

All study-drug-related AEs, AEs with an outcome of death, AEs leading to permanent discontinuation of treatment will be listed with all their details. Time from the treatment start for serelaxin group or from randomization for Standard of Care group, to the AE start/end date, will be also computed. Elapsed days, hours and minutes plus 1 minute will be reported on the listing.

In case of an ongoing event, no days relative to the end of the event will be computed.

In case of missing time of start or end of an event, no relative days will be computed.

Safety risks and events of interest

Adverse events will be also presented according to the search strategies using the latest MedDRA dictionary version available before database lock, as specified in the Case Retrieval Strategy (CRS) defined by Novartis. Adverse events will be characterized as safety risks and as events of interest according to the rules specified in Table 5.3-1 and Table 5.3-2, respectively.

Safety risks and events of interest through Day 5 and Day 14 will be summarized by treatment group and tabulated by safety risk / events of interest, NMQ, HLGT, SMQ or SOC, and Preferred Term of MedDRA dictionary. Absolute and relative frequency of patients who have experienced each type of event will be presented.

Table 5.3-1: MedDRA* search specifications to evaluate safety risks

Safety Risk	Specification
Hypotension (identified)	NMQ 'Hypotension' (Broad)
Hemoglobin/ hematocrit transient decrease (potential)	*CMQ 'Hemoglobin/ hematocrit transient decrease'* • SMQ 'Haemorrhages' (Broad) • HLGT 'Anaemias nonhaemolytic and marrow depression' • SMQ 'Haematopoietic erythropenia' (Broad)
Fetotoxicity and teratogenicity (potential)	SMQ 'Pregnancy and neonatal topics' (Broad)

CMQ: Customized MedDRA query; HLGT: High level group term; NMQ: Novartis MedDRA query; SMQ: Standardized MedDRA query.

* According to MedDRA v19.1. Specifications could possibly change before database lock.

Table 5.3-2: MedDRA* search specifications to evaluate events of interest

Event of Interest	Specification
Menorrhagia/Metrorrhagia	HLGT 'Menstrual cycle and uterine bleeding disorders'
Hypokalemia	NMQ 'Hypokalemia' (Broad)
Hypersensitivity/Immunogenicity	*CMQ 'Hypersensitivity, Immunogenicity, Cutaneous reactions':* • SMQ 'Hypersensitivity' (Broad) • SMQ 'Angioedema' (Broad) • SMQ 'Anaphylactic reaction' (Broad) • SOC 'Immune system disorders' • HLGT 'Immunology and allergy investigations' • HLGT 'Administration site reactions' • SMQ 'Severe cutaneous adverse reactions' (Broad)
Cardiac failure	SMQ 'Cardiac failure' (Broad)
QT prolongation	*CMQ 'Cardiac arrhythmias/QT prolongation':* • SMQ 'Torsade de pointes/QT prolongation' (Broad) • SMQ 'Cardiac arrhythmias' (Broad)
Thromboembolic events	SMQ 'Embolic and thrombotic events' (Broad)
Renal impairment	*CMQ 'Renal impairment':* • SMQ 'Acute renal failure' (Broad) • PT 'Chronic kidney disease'
Respiratory failure	SMQ 'Respiratory failure' (Broad)
Hepatotoxicity	SMQ 'Drug related hepatic disorders – comprehensive search' (Broad)
Potential promotion of cancers	SMQ 'Malignancies' (Broad)

CMQ: Customized MedDRA query; HLGT: High level group term; NMQ: Novartis MedDRA query; SMQ: Standardized MedDRA query; SOC: System organ class.

* According to MedDRA v19.1. Specifications could possibly change before database lock.

Liver events

Liver events are a subgroup of Adverse Events.

As a patient may have more than one liver event the total number of liver events could be greater than the total number of patients. The number of subjects with 0, 1, 2, >2 liver events will be summarized by treatment. Summary statistics on data about liver events will be provided by treatment.

Liver events details, collected in the "Liver Event - Overview" section and including medical history possibly contributing to liver dysfunction, alcohol consumption, drug abuse and acetaminophen/paracetamol intake, will be described presenting absolute and relative frequencies of liver events in each category of variable (percentages will be calculated on the total of liver events with non-missing information).

Imaging, pathology, autoimmune and viral serology assessments will be presented with the total of liver events; results will be presented by each procedure and percentages will be calculated on each procedure with non-missing information.

Vital signs

Vital signs evaluations will include measurements of body weight (Kilogram), body mass index (kg/m^2), height (cm) at screening, body temperature (Celsius), respiratory rate (Breath/min), pulse (Beats/min) and systolic and diastolic blood pressure (mmHg). Conversions from different units will be performed as aforementioned (see Section 5.1).

Summary statistics (i.e., number of observations, mean, standard deviation, median, first and third quartiles, minimum and maximum) of raw data and change (absolute and %) from screening (i.e., start of screening for all parameters and end of screening only for pulse and blood pressure) will be provided at each assessment time point. Treatment groups will be compared for changes (absolute) from screening (i.e., start and end, where applicable) for each parameter. The estimated difference between treatment groups and 95% CI will be presented.

For serelaxin group only, descriptive statistics of raw data and change (absolute and %) versus the pre-dose value will also be provided for heart rate (Beats/min) and systolic and diastolic blood pressure (mmHg) collected for drug infusion and post-drug infusion monitoring.

Summary statistics for raw data, absolute change and percentage change from screening, and absolute change and percentage change from Day 5 will be provided by treatment group for heart rate (Beats/min), systolic and diastolic blood pressure (mmHg) collected daily through the hospitalization (after Day 5 and up to Day 29).

Line plots of the mean and standard error of systolic and diastolic blood pressure over time by treatment group will be provided.

Laboratory data: hematology and chemistry

Summary statistics of raw data and change (absolute and %) from screening at each scheduled visit and for each laboratory parameter will be presented by treatment group. Laboratory data will be analysed and presented considering the preferred unit of measurement. Treatment groups will be compared for changes (absolute) from screening for each parameter. The estimated difference between treatment groups and 95% CI will be presented.

Laboratory data will also be summarized by presenting for each laboratory parameter shift tables showing the pattern of change from screening versus each post-screening visit, based on the cross-classification of the number and percentage of subjects in each treatment group with any post-screening value that is below [low], within [normal], above [high], below&above [low&high] the normal ranges.

Abnormal laboratory values will be presented for each subject in a data listing with an indication of whether the value is above (H) or below (L) the normal reference range and if it is notable.

The categorical analysis for laboratory parameters will be presented using the criteria reported in Table 5.3-3. The number and percentage of subjects meeting each specified criterion will be tabulated by visit and for any post-baseline visit. For those criteria with the specified cut off point (e.g., < or > x.x), the summary statistics will be presented for baseline and each post-baseline visit, with the denominator including those subjects with evaluable measurements at the specified visits. For criteria with specification regarding the relative change from baseline, the summary statistics will be presented for each post-baseline visit with the denominator including those subjects with evaluable measurements at both baseline and the corresponding post-baseline visit.

Table 5.3-3: Categorical analysis for laboratory parameters

	Parameter categories	Criterion
Hematology	Red blood cell counts (RBC)	>50% increase >20% decrease <2.5x10^6/uL >8.5x10^6/uL
	Hemoglobin	>50% increase >20% decrease >20 g/dL <8 g/dL
	Hematocrit	>50% increase >20% decrease <20% >60%
	RBC, Hemoglobin, & Hematocrit	RBC > 20% decrease AND Hemoglobin > 20% decrease AND Hematocrit > 20% decrease
	White blood cell counts (WBC)	>100% increase >50% decrease <3.5x10^9/L >25x10^9/L
	Platelet	>75% increase >50% decrease <50x10^9/UL >600x10^9/UL
	Neutrophils	<1.5x10^9/L <1.0x10^9/L
	Lymphocytes	None
Serum Chemistry	Blood Urea Nitrogen (BUN)	>100% increase >14.28 mmol/L
	Creatinine	>100% increase >50% increase Increase of >=0.3 mg/dL Increase of >=0.5 mg/dL Increase of >=1.0 mg/dL >2 mg/dL >2.5 mg/dL
	Estimated Glomerular Filtration Rate (eGFR)	Decrease of >25% Decrease of >50% Decrease of >30mL/min/1.73m^2
	Potassium	>6 mmol/L >5.5 mmol/L <3.0 mmol/L
	Calcium	<1.75 mmol/L >3.1 mmol/L
	Sodium	<120 mmol/L <130 mmol/L >155 mmol/L

In addition, for the liver function test (LFT), summary table will be provided on the number and proportion of patients having the criteria defined in Table 5.3-4. These are evaluated at each post-baseline visit as well as at any post-baseline visit. The data are summarized using two approaches:

1. Patients with newly occurring abnormalities, defined as events occurring post baseline for patients who did not meet the abnormal criteria at baseline (Table 5.3-4).

2. Patients with abnormalities post baseline, regardless of the baseline values (Table 5.3-5).

Table 5.3-4: LFT categorical analysis ('newly occurring')

Category family	Category - Numerator Subjects at risk meeting the criteria at post BL	Denominator Subjects at risk and meeting the following criteria at BL
ALT/AST	ALT or AST >3x ULN	Subjects with ALT and AST ≤3x ULN at BL
	ALT or AST >5x ULN	
	ALT or AST >8x ULN	
	ALT or AST >10x ULN	
Hy's chemistry category	ALT or AST >3x ULN and TBL >1.5x ULN	Subjects with ALT and AST ≤3x ULN at BL
	ALT or AST >3x ULN and TBL >2x ULN	
	ALT or AST >5x ULN and TBL >2x ULN	
	ALT or AST >8x ULN and TBL >2x ULN	
	ALT or AST >10x ULN and TBL >2x ULN	
	ALT or AST >3xULN and TBL >2x ULN and ALP <2x ULN	
TBL & ALP	TBL >1.5x ULN and ALP >2x ULN	Subjects with TBL ≤1.5x ULN and ALP ≤2x ULN at BL
	TBL >2x ULN and ALP >2x ULN	*(comment: the intention is that both parameters must below threshold)*
Isolated TBL	TBL >1.5x ULN & ALT and AST ≤3x ULN and ALP ≤2x ULN	Subjects with TBL ≤1.5x ULN & ALT and AST ≤3x ULN and ALP ≤2x ULN
	TBL >2x ULN & ALT and AST ≤3x ULN and ALP ≤2x ULN	*(comment: same denominator as for 'isolated ALP')*
	TBL >3x ULN & ALT and AST ≤3x ULN and ALP ≤2x ULN	
Isolated ALP	ALP >2x ULN & ALT and AST ≤3x ULN and TBL ≤1.5x ULN	Subjects with ALP ≤2x ULN & ALT and AST ≤3x ULN and TBL ≤1.5x ULN
	ALP >3x ULN & ALT and AST ≤3x ULN and TBL ≤1.5x ULN	*(comment: same denominator as for 'isolated TBL')*
	ALP >5x ULN & ALT and AST ≤3x ULN and TBL ≤1.5x ULN	

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBL: total bilirubin; ULN: upper limit of normal.

Table 5.3-5: LFT categorical analysis ('any post-baseline elevation')

Category family	Category - Numerator Subjects at risk meeting the criteria at post BL	Denominator Subjects at risk
ALT/AST	ALT or AST >3x ULN	Subjects with a post BL value
	ALT or AST >5x ULN	
	ALT or AST >8x ULN	
	ALT or AST >10x ULN	
Hy's chemistry category	ALT or AST >3x ULN and TBL >1.5x ULN	
	ALT or AST >3x ULN and TBL >2x ULN	
	ALT or AST >5x ULN and TBL >2x ULN	
	ALT or AST >8x ULN and TBL >2x ULN	
	ALT or AST >10x ULN and TBL >2x ULN	
	ALT or AST >3xULN and TBL >2x ULN and ALP <2x ULN	
TBL & ALP	TBL >1.5x ULN and ALP >2x ULN	
	TBL >2x ULN and ALP >2x ULN	
Isolated TBL	TBL >1.5x ULN & ALT and AST ≤3x ULN and ALP≤2x ULN	
	TBL >2x ULN & ALT and AST ≤3x ULN and ALP ≤2x ULN	
	TBL >3x ULN & ALT and AST ≤3x ULN and ALP ≤2x ULN	
Isolated ALP	ALP >2x ULN & ALT and AST ≤3x ULN and TBL ≤1.5x ULN	
	ALP >3x ULN & ALT and AST ≤3x ULN and TBL ≤1.5x ULN	
	ALP >5x ULN & ALT and AST ≤3x ULN and TBL ≤1.5x ULN	

Plots showing the relationship between maximum TBL and ALT or AST at any visit (eDISH plot for the evaluation of drug-induced serious hepatotoxicity) will also be provided.

Laboratory data: urinalysis

Summary statistics for data about urinalysis will be provided at each assessment time point by treatment group. For each parameter result, absolute and relative frequencies of patients reporting it will be provided. Percentages will be computed considering patients with non-missing information at each assessment time point.

Electrocardiogram (ECG)

The number and proportion of patients by procedure performed and overall interpretation will be provided at each assessment time point by treatment group. Percentages will be computed considering patients with non-missing information at each assessment time point. Summary statistics will be provided at each assessment time point by treatment group.

Heart rate (beats/min), mean PR duration (msec), mean QT duration (msec), corrected QT Fridericia interval (QTcF) and mean QRS duration (msec) will be described, providing number of observations, mean, standard deviation, median, first and third quartiles, minimum and maximum at each assessment time point by treatment group.

The number and proportion of patients with the following criteria at any post-baseline visit will be presented:

Table 5.3-6: Criteria for ECG categorical analysis

Topic	Parameter categories	Criterion for denominator
QT/QTcF	QT/QTcF >450 msec	Subjects with QT/QTcF ≤450 msec at BL
	QT/QTcF >480 msec	Subjects with QT/QTcF ≤480 msec at BL
	QT/QTcF >500 msec	Subjects with QT/QTcF ≤500 msec at BL
	QT/QTcF >450 msec; males only	Male subjects with QT/QTcF ≤450 msec at BL
	QT/QTcF >460 msec; females only	Female subjects with QT/QTcF ≤460 msec at BL
	QT/QTcF increase from BL >30 msec	Subjects with a non-missing value at BL and post BL
	QT/QTcF increase from BL >60 msec	Subjects with a non-missing value at BL and post BL
PR	PR >200 msec	Subjects with PR ≤200 msec at BL
	PR >220 msec	Subjects with PR ≤220 msec at BL
	PR > 200 msec and change from BL ≥25%	Subjects with PR ≤200 msec at BL
QRS	QRS >110 msec and change from BL ≥25%	Subjects with QRS ≤110 msec at BL
	QRS >120 msec and change from BL ≥25%	Subjects with QRS ≤120 msec at BL
Heart Rate	Heart rate >100 bpm and change from BL ≥25%	Subjects with heart rate ≤100 bpm at BL
	Heart rate <50 bpm and change from BL ≥25%	Subjects with heart rate ≥50 bpm at BL

In addition, shift tables comparing baseline ECG overall interpretation (normal, clinically insignificant abnormality, clinically significant abnormality) with Day 5/discharge ECG overall interpretation (normal, clinically insignificant abnormality, clinically significant abnormality) will be provided by treatment group.

A listing of clinically significant abnormalities in ECG evaluations will be provided.

Echocardiography

Echocardiography is not considered as study related procedures and is performed according to local diagnostic practice.

Overall interpretation will be described by providing the number and proportion of subjects in each category at each assessment time point by treatment group. Percentages will be computed considering patients with non-missing information at each assessment time point.

LV Ejection Fraction (%) will be described by means of summary statistics (i.e., number of observations, mean, standard deviation, median, first and third quartiles, minimum and maximum) at each assessment time point by treatment group.

Systolic blood pressure decrease event

A confirmed systolic blood pressure decrease event (CBPDE) is defined as systolic blood pressure decreases by > 40 mmHg from just before the study drug infusion at baseline but is ≥ 100 mmHg in 2 consecutive measurements 15 minutes apart, or if in 2 consecutive measurements 15 minutes apart, systolic blood pressure reduces to < 100 mmHg, as reported in the "Systolic blood pressure decrease event – vital signs" eCRF.

For the serelaxin arm only, the number and proportion of patients who experienced a confirmed systolic blood pressure decrease event during study drug administration will be provided. Percentages will be computed considering patients in the analysis population.

The number and proportion of patients who experienced 0, 1, 2, >2 confirmed systolic blood pressure decrease events will be provided together with the number and proportion of patients who experienced asymptomatic/symptomatic events (as recorded on the "Systolic Blood pressure Decrease Event" eCRF page).

The total number of events will be further characterized, showing absolute and relative frequencies of events for the following characteristics:

- Outcome: not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown
- Action taken with study treatment: none, dose adjusted but not discontinued, permanently discontinued, dose adjusted then permanently discontinued

  The category of "dose adjusted then permanently discontinued" for action taken is derived by combining the categories "dose adjusted but not discontinued" and "permanently discontinued" when recorded separately in the eCRF for the same CBPDE.
- Medications or therapies taken: yes or no, if yes type of medication/therapy (fluids/crystalloids, inotropes, vasopressors, circulatory support, mechanical ventilation, other)

Percentages will be computed considering events with non-missing information.

The number and proportion of patients who experienced at least one confirmed systolic blood pressure decrease events will be also presented by outcome, action taken and medications/therapies taken.

The number and proportion of patients who experienced at least one systolic blood pressure decrease events will be also presented by type of event in terms of SBP onset value (mmHg):

- if systolic blood pressure decreased by > 40 mmHg from baseline but was ≥ 100 mmHg;
- if systolic blood pressure reduced to < 100 mmHg.

The SBP value (mmHg) at baseline (i.e., at randomization) will be summarized for patients with a confirmed SBP decrease event and for those without a confirmed SBP decrease event.

The following summaries will be presented for patients with a confirmed SBP decrease event:

- Time (hours) to first CBPDE, defined as time from randomization date and time to the first CBPDE date and time + 1 minute
- SBP (mmHg) decrease from baseline to first CBPDE
- Trough SBP (mmHg) since CBPDE, defined as the minimum of SBP values recorded during the study including the measurements occurred before CBPDE
- SBP (mmHg) decrease from baseline to trough, where the trough SBP is the minimum value recorded for any CBPDE

Summary statistics will be provided for heart rate (Beats/min) and systolic and diastolic blood pressure (mmHg) at each assessment time point following the first event onset. Summaries of heart rate, SBP and DBP will be provided separately for those confirmed events (both symptomatic and asymptomatic, as recorded on the eCRF) that resulted in study drug dose reduction but not discontinuation, those that resulted in study drug discontinuation, and those that resulted in study drug dose reduction then permanent discontinuation.

The possible interaction between the effect of serelaxin and the effect of IV nitrate administration within the first 48 hours will be examined by providing the number and proportion of patients who experienced at least one confirmed systolic blood pressure decrease event split by intake of IV nitrate within 48 hours (i.e., subgroup of patients without any intake of IV nitrate within 48 hours vs. subgroup of patients with at least one intake of IV nitrate within 48 hours). A subject with at least one intake of IV nitrate within 48 hours is defined as a subject who:

- was on IV nitrates at the time of randomization (eCRF section “Index Heart Failure Hospitalization”);
- started new IV nitrates, restarted IV nitrates, or increased dose of IV nitrates (e.g., isosorbide dinitrate, nitroglycerine, sodium nitroprusside) as a consequence of WHF while still under serelaxin infusion (eCRF section “Clinical Worsening of Heart Failure (Endpoint to be adjudicated)”).

Category of patients with at least one confirmed systolic blood pressure decrease event CBPDE/ no CBPDE will be compared between categories with a Chi-Square test. In case of cell frequencies less than 5, Fisher’s Exact test will be used. Category of patients with at least one asymptomatic CBPDE / at least one symptomatic CBPDE / no CBPDE will be compared between categories with a Chi-Square test. In case of cell frequencies less than 5, Fisher’s Exact test will be used. Cochran-Armitage Test for trend will also be performed.

To further investigate the impact of CBPDE, the following analyses will be performed:

- baseline characteristics by CBPDE (yes/no);

- concomitant medications by CBPDE (yes/no);
- worsening heart failure/all cause death through Day 5 by CBPDE (yes/no) and by CBPDE impact on study drug administration (dose decreased but not discontinued, or study drug discontinued, or both);
- adverse events through Day 5 and through Day 14 by CBPDE (yes/no)

Causes that lead to a re-hospitalization or emergency/urgent care >24 hours not resulting in admission

In case the reason for re-hospitalization or emergency/urgent care >24 hours not resulting in admission is HF, renal impairment, or cardiac (chest pain, ACS, MI), further details are collected in dedicated eCRF sections ("Rehospitalization information", "Heart failure details", "Acute MI/ACS/chest pain" and "Renal failure").

Data will be summarized presenting absolute and relative frequencies (percentages calculated on events with non-missing information) for discrete variables; presenting number of observations, mean, standard deviation, median, first and third quartiles, minimum and maximum for continuous variables.

Survival and Death information

Descriptive statistics by treatment group will be presented for death information.

All deaths occurred will be listed with all their details.

Pregnancy test results

Any pregnancies reported will be listed and outcome reported.

5.4. INTERIM ANALYSIS

No formal interim analyses are planned.

An external independent Data Monitoring Committee (DMC) is appointed to monitor the safety of study participants and to ensure that the program is conducted with highest scientific and ethical standards. This DMC will review the safety data and data relating to the primary efficacy endpoint throughout the trial and make safety recommendations on the conduct of the trial. The committee will not provide recommendations based on the efficacy analysis. No consequent early termination or sample size adjustment will be based on the DMC-related efficacy analysis. In case the recommendations are considered to have significant bearing on the benefit-risk of the trial, these will be communicated by DMC to Executive Committee members and Novartis. The final decisions will be communicated to the investigators within an appropriate timeframe.

6. APPENDIX

Appendix I: Table of Conversion Factor for Laboratory Parameters.