

Clinical Development & Medical Affairs

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**

Authors:

[REDACTED]

Principal or Coordinating Investigator

[REDACTED] for the RLX030A3301 Executive Committee

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## List of abbreviations

ACE	Angiotensin-Converting Enzyme
AE	Adverse Event
AHF	Acute Heart Failure
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
CCU	Critical Care Unit
CEC	Central Event Committee
cGMP	cyclic Guanosine Monophosphate
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report/Record Form (paper)
CRO	Contract Research Organization
CSR	Clinical Study Report
CV	Cardiovascular
DB	Double Blind
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form/Record Form
ED	Emergency Department
EDC	Electronic Data Capture
EGFR	Estimated Glomerular Filtration Rate
EMS	Emergency Medical Services
ER	Emergency Room
ET-B	Endothelin receptor Type B
FAS	Full Analysis Set
GDF-15	Growth Differentiation Factor 15
GI	Gastro-Intestinal



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HF	Heart Failure
H-FABP	Heart-type Fatty Acid-Binding Protein
HPA	Hypothalamus-Pituitary-Adrenal
HR	Heart Rate
HRQoL	Health Related Quality of Life
HRU	Health Care Resource Utilization
IB	Investigator's Brochure
ICF	Informed Consent Form
ICU	Intensive Care Unit
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Randomization Technology
ITT	Intent-to-Treat
IV	Intravenous
JVP	Jugular Venous Pulse
LC-MS/MS	Liquid Chromatography Tandem Mass Spectrometry
LFT	Liver Function Test
LOS	Length of Stay
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
NGAL	Neutrophil Gelatinase Associated Lipocalin
NO/NOx	Nitric Oxide
NOS	Nitric Oxide Synthase
NT-proBNP	N-Terminal pro b-type Natriuretic Peptide
OL	Open Label
PP	Per Protocol
PT	Preferred Term
PTX-3	Pentraxin-3
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event



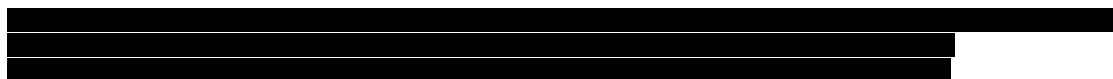
SD	Standard Deviation
SBP	Systolic Blood Pressure
sMDRD	Simplified Modification of Diet in Renal Disease
SOC	Standard of Care; System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total Bilirubin
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
VAS AUC	Visual Analog Scale Area Under the Curve
WHF	Worsening Heart Failure
WOCBP	Women of Child Bearing Potential





## Glossary of terms

<b>Assessment</b>	A procedure used to generate data required by the study
<b>Enrollment</b>	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
<b>Epoch</b>	The planned stage of the subjects' participation in the study. Each epoch serves a purpose in the study as a whole. Typical epochs are: determination of subject eligibility, wash-out of previous treatments, exposure of subject to treatment or to follow-up after treatment has ended.
<b>Investigational drug</b>	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product".
<b>Investigational treatment</b>	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls.  This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination.  Investigational treatment generally <i>does not include</i> other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage
<b>Medication number</b>	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
<b>Part</b>	A subdivision of a single protocol into major design components. These parts often are independent of each other and have different populations or objectives. For example, a single dose design, a multiple dose design that are combined into one protocol, or the same design with different patient populations in each part.
<b>Period</b>	A subdivision of a cross-over study
<b>Premature patient withdrawal</b>	Point/time when the patient exits from the study prior to the planned completion of all investigational/study treatment administration and all assessments (including follow-up)
<b>Randomization number</b>	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
<b>Stop study participation</b>	Point/time at which the patient came in for a final evaluation visit or when study/investigational treatment was discontinued whichever is later
<b>Study drug/treatment</b>	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
<b>Study/investigational treatment discontinuation</b>	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
<b>Subject Number</b>	A number assigned to each patient who enrolls into the study
<b>Variable</b>	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points.



## **Amendment 4**

### **Amendment rationale**

This amendment to the protocol is necessary because the Executive Committee recommended during its meeting held on 15<sup>th</sup> of June 2016 to increase the number of randomized patients from 2,685 to 3,183 patients. This decision was endorsed by the Data Monitoring Committee (DMC) during the meeting on 21<sup>st</sup> of June 2016. The rationale for the increase in sample size is provided below.

Although the rate of enrollment into the trial is in line with the planning, the number of events constitutive of the primary endpoint (i.e. patients with WHF events or death through Day 5) is lower than expected.

[REDACTED]

[REDACTED]

### ***Ancillary changes introduced with the amendment***

#### **Clarification in reporting Adverse Events and Worsening of Heart Failure events**

In-hospital Worsening of Heart Failure (WHF) within the first 5 days is one of two components of the primary endpoint. Some WHF events could represent an endpoint as well as a non-serious or serious AE.

In order to avoid potential under-reporting of non-serious AEs indicative of cardiac failure due to inconsistency in event reporting by investigators, the WHF event and/or the related signs and symptoms should be always recorded on the Adverse Event eCRF page.

#### **Patients treated with valsartan/sacubitril**

When a patient treated with valsartan/sacubitril (Entresto<sup>®</sup>) is considered for randomization in the trial, only NT-proBNP, and not BNP, should be assessed during the screening phase.

As reported in the SmPC (Summary of Product Characteristics) of Entresto<sup>®</sup>, BNP is not a suitable biomarker of heart failure in patients treated with Entresto<sup>®</sup> because BNP is a neprilysin substrate. NT-proBNP is not a neprilysin substrate and is therefore a more suitable biomarker.

[REDACTED]



So far, more than two thousand three hundred and thirty (2337) patients have been randomized by Austria, Belgium, Bulgaria, Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Switzerland and United Kingdom in the study.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions. A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

### Changes to the protocol

**Section 4.1 and Table 6.1** updated to clarify that only NT-proBNP should be assessed in patients under valsartan/sacubitril (Entresto<sup>®</sup>) therapy

**Section 5.4** updated to clarify the management of the treatment blinding in the study

**Section 6.5.4** updated to clarify the volume of the blood sample collection.

**Section 7** updated to clarify the correct reporting of Worsening of Heart Failure events versus Adverse Events.

**Section 9.7** updated in the sample size calculation.

### Amendment 3

#### Amendment rationale

Acute Heart Failure is a complex and subjective clinical diagnosis. Since the diagnosis of AHF is primarily based on clinical observations that are interpreted bedside, in an urgent care environment, based on the clinical judgment of the investigator, the diagnosis is sometimes difficult to qualify.

Therefore, the study Executive Committee has recommended changes to better specify the criteria defining AHF in the patient population under investigation, correct inconsistencies and improve the overall clarity of the study. This has led to the following adjustments in inclusion and exclusion criteria:

- Increase of required NT-proBNP level for inclusion of a patient from 1,400 to 2,000 pg/mL in order to ensure that patients with cardiac dyspnea are included
- Exclusion of patients with SBP above 180 mmHg at the end of screening in order to avoid pure hypertensive crisis
- To ensure that patients suffering from non-cardiogenic dyspnea are not enrolled into RELAX-AHF-EU to ensure that patients with cardiac dyspnea are included, another

criteria has been added, the exclusion of patients with a known history of respiratory disorder (i.e. COPD) requiring the daily use of IV steroids.

- To ensure that an underlying malignancy does not interfere with the efficacy objectives (e.g. no treatment success) and to collect SAEs/safety data that are due the disease condition and/or the allocated study treatment and not associated with the malignancy, the exclusion of patients with history of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated (within the past year).

### ***Other changes in the protocol***

- The possibility to use a BNP level rather than a NT-proBNP level for inclusion of the patient into the study will be introduced with the present amendment. At the start of the study, all sites without a local possibility to assess NT-proBNP levels were equipped with a bedside device of NT-proBNP assessment, the COBAS device. Feedback from a number of sites was that they would like to use their local laboratory to assess natriuretic peptide levels in order to gain time. Since some of these local laboratories only measure BNP levels, the possibility to include patients based on BNP  $\geq 500$  pg/mL will now be added to the inclusion criteria

- [REDACTED]

### **Study Status**

The recruitment in the study is ongoing.

So far, more than one thousand (1000) patients have been randomized by Austria, Belgium, Bulgaria, Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Switzerland and United Kingdom in the study.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions. A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

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### **Changes to the protocol**

#### **Section 4.1: Inclusion criteria**

No. 4: NT-proBNP criterion has been increased to  $\geq 2,000$  pg/mL, and BNP criterion  $\geq 500$  pg/mL has been added.

#### **Section 4.2: Exclusion criteria**

The following exclusion criteria have been added:

[REDACTED]

No. 2: 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.

No. 3: Patients with systolic blood pressure >180 mmHg at the end of screening or persistent heart rate >130 bpm.

No. 13: History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated (within the past year) has been added.

The following exclusion criteria have been updated:

No. 5: *Diuretic* has been added to the description of equivalent for IV furosemide. The use of IV nitrates is permitted if the patient has systolic BP >150 mmHg at “*the start of screening*”.

**Section 5.3** updated to clarify the management of mis-randomized patients.

**Sections 5.5.9 and 5.5.10** updated to clarify patient withdrawal and continued patient follow-up.

**Section 6.4.1.1** modified to indicate who, besides the PI, can assess AHF signs and symptoms.

[REDACTED]

[REDACTED]

**Section 6.5.2 and Table 6-1** updated to clarify the time points for the collection of vital signs.

**Section 6.6.4** clarifies the procedure for administering the EQ-5D-5L questionnaire.

**Section 6.6.6:** Echocardiography has been added to collect and record (into eCRF) the most recent data in the past 12 months if the evaluation is performed and the values obtained are available in the source documents.

**Section 7.2:** SUSAR reporting has been updated to clarify that pre-specified AEs commonly observed in the study population that also meet the criteria for SUSARs will be expedited to Health Authority (if specifically requested by local health authority). Investigator Notifications (INs) will not be issued for these events.

**Sections 6, 6.4.1.1, 6.5.1, 6.5.2, 6.5.3, 6.5.4, and Table 6-1** provide clarity and flexibility regarding the conduct and timing of the study visits and visit procedures.

**Section 9** provides clarity on data analysis.

## Amendment 2

### Amendment rationale

This amendment is introduced based on the initial feedback gathered from the investigators already screening and recruiting patients, the request for clarification from some local health authorities, and further discussions with the Executive Committee Board. These changes aim

[REDACTED]

at further strengthening the protocol, facilitating the recruitment and ensuring possible data merging with other serelaxin studies like RELAX-AHF-2.

The key changes introduced in this amendment are the following:

- More background information has been provided about the clinical parameter in-hospital WHF-worsening of heart failure.
- The inclusion criterion “pulmonary congestion” is now to be diagnosed by physical examination and chest X-ray as required by local clinical practice. Echocardiography is not anymore mentioned as a possible procedure for diagnosis of pulmonary congestion.
- Refinement of inclusion of patients with renal dysfunction. Patients with significant renal dysfunction are most at risk of complicated AHF episodes. Concomitantly, these patients benefit potentially most from serelaxin, as shown by the available data. To ensure that these patients represent a large enough proportion in this practical trial, it was decided to allow inclusion of patients with an eGFR of 25 to 75 ml/min/1.73m<sup>2</sup> (instead of 30 to 75 ml/min/1.73m<sup>2</sup>).
- Streamline the exclusion criteria related to WOCBP changing the requirements from “effective” to “highly effective” methods of contraception to minimize the likelihood of pregnancies during dosing and for 5 days after cessation of study drug.
- A discharge assessment was added to collect valuable information about the real life clinical situation when the patient is sent back home. It has been shown that 24% of patients hospitalized for HF in Europe have signs of congestion at discharge ([Maggioni et al 2010](#)). The primary endpoint is through Day 5, and we expect most patients to be discharged later than Day 5. The added discharge assessment would capture novel information about the residual AHF signs at discharge (and before the FU visit at Day 14).
- The primary endpoint “time to in hospital WHF or death at Day 5” has been strengthened in that the time window allowed for in hospital WHF assessment is through Day 5 (which was previously +/- 1 day).
- Exclusion of patients with a body weight below 40 kg and >160 kg, which would have underlying medical conditions that would render this treatment most probably not effective in these two groups, for different reasons, the former (the first are a very selected subgroup of cachectic HF patients, the latter group of patients, expect to be very few in European countries) would have major associated dysmetabolic conditions.
- Exclusion criterion number #03 was clarified: it will now require that concomitant active therapies or procedures are not allowed “2 hours prior to *randomization*” (and not as was previously “2 hours prior to *screening*”).
- The HIV, HBV and HCV testing of active or latent HIV, HBV or HCV infection were suppressed, based on current epidemiology and the available reassuring data, showing no signal of concern in terms of safety and tolerability.
- The exclusion criterion of severe pulmonary disease is now deleted. It is already contained in the exclusion criteria #01 “dyspnea primarily due to non-cardiac causes” and exclusion criteria #16 (when patient is put at risk or deemed unsuitable for the study).

Additional points are also clarified through this amendment:

- The justification for the open label design has been expanded



- Time points at which vital signs are to be assessed, in patients randomized to Standard of Care (SOC) as compared to the serelaxin group. It now highlights that the reference time point for the assessments required in the serelaxin group is “start of the infusion”, whereas it is the “randomization time point” for the SOC group.
- The handling of the serelaxin infusion when concomitant AHF therapies have to be started during the serelaxin infusion is clarified.
- The SBP measurements between screening and randomization and implications on serelaxin infusion were clarified.
- The term mechanical ventilation, and the different categories of invasive and non-invasive assisted ventilation, are better defined.
- The collection of EQ-5D-5L HRQOL questionnaires at Day 2 has been added.

## **Study Status**

The recruitment in the study is ongoing.

So far, sixty-nine (69) patients have been randomized by Belgium, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Russia, Slovakia and United Kingdom in the study.

## **Changes to the protocol**

### **Section 1**

Text added to strengthen a meaningful definition of Worsening Heart Failure (WHF) and its significance for patients’ disease trajectory underlying the results of RELAX-AHF study in term of WHF.

### **Figure 3.1**

Figure modified to correct inconsistencies with the rest of Section 3.1.

### **Section 3.2**

Choice of Open-label design strengthened by adding details of pros and cons of an open-label design versus a double-blind design in Randomized Controlled Trials (RCT).

### **Section 4.1**

Some changes to key inclusion criteria.

### **Section 4.2**

Some changes to key exclusion criteria.

### **Section 5.5.4**

Sentences added to align with the current version of the pharmacist manual.

### **Section 5.5.5**

Instructions provided to clarify what to do in case of Systolic Blood Pressure (SBP) drop between randomization and start of serelaxin infusion.





### **Section 5.5.7**

Instructions provided to clarify what to do in case IV therapies have to be administered after randomization in both arms.

### **Section 5.5.8**

Section amended to be consistent with the previous Section.

### **Section 6**

Section amended to restrict the visit window of Day 5 (time point of the main efficacy endpoint).

### **Table 6.1**

Table and footnotes amended to introduce a discharge visit if the patient is still hospitalized beyond Day 5, clarify whose frequency all the assessments will be performed in the Standard of Care (SoC) arm.

### **Section 8.5**

Text amended to be consistent with the current version of the Clinical Endpoint Committee charter.

### **Section 9.5.1**

Header amended to be consistent with the corresponding efficacy variable mentioned in Section 6.4.1.

### **Table 14.1 and Table 14.2**

Tables amended to align the liver events monitoring according to the new Novartis liver guidance.

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A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

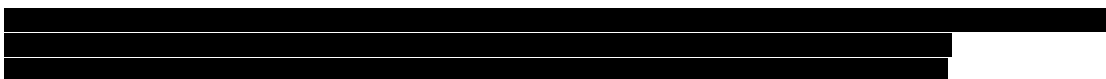
The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes here in affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

## **Amendment 1 (for Germany ONLY)**

### **Amendment rationale**

This amendment is being initiated at the request of German Health Authorities & will be applicable only to German sites participating in this trial. As part of the review process, German health authorities have requested to amend the protocol with inclusion of the following 2 requirements:



1. As part of additional safety measures & to avoid any potential risk of hypotension with the infusion of serelaxin, it was recommended to clarify the use of an infusion pump, a drip or any other controllable infusion systems to ensure a constant infusion rate of serelaxin at 10ml/hour.
2. To further clarify the informed consent procedure related to the nature of the witness, an “independent second physician or nurse” is being added who will co-sign the ICF & thereby confirm that the patient has provided informed consent according to his/her own will following receipt of all study related information based on his/her ability to understand the trial procedures.

### **Study status**

The recruitment in the study has just started.

So far, one patient has been screened and randomized in Italy.

### **Changes to the protocol**

#### **Section 1**

Text corrected to remove the reference to the status of the Marketing Authorization Application for serelaxin.

#### **Section 5.5.4**

Text added to specify how the infusion of the study drug will be maintained constant at a rate of 10 mL/hour.

#### **Section 7.2**

Text corrected to make reference to the most recent European Commission communication.

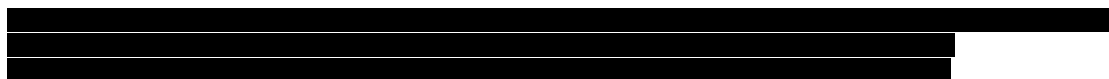
#### **Section 10.2**

Text added to clarify the independence of the witness from the trial group during the informed consent procedure

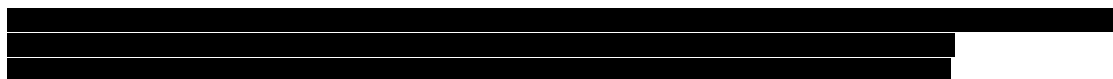


## Protocol synopsis

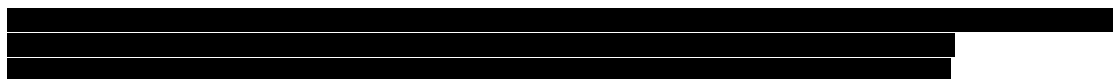
<b>Protocol number</b>	CRLX030A3301
<b>Title</b>	A multicenter, prospective, randomized, open label study to assess the effect of serelaxin versus standard of care in acute heart failure (AHF) patients.
<b>Brief title</b>	Effect of serelaxin versus standard of care in acute heart failure (AHF) patients.
<b>Sponsor and Clinical Phase</b>	Novartis, IIIb
<b>Investigation type</b>	Drug
<b>Study type</b>	Interventional
<b>Purpose and rationale</b>	<p>The aim of this study is to assess the efficacy, safety and tolerability of intravenous infusion of 30 µg/kg/day serelaxin administered for 48 hours, when added to standard therapy in patients hospitalized for acute heart failure. Efficacy will be determined based on the combined primary end-point of in-hospital worsening of heart failure requiring rescue therapy and all-cause death through Day 5. Patients will be followed-up for 30 days.</p> <p>The aim of this study is to generate clinical evidence, especially on the short-term period (in-hospital and at 30 days) that will complement existing and future serelaxin data sets in AHF.</p>
<b>Primary Objective(s) and Key Secondary Objective</b>	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.
<b>Secondary Objectives</b>	<p>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.</p> <p>To assess the effect of serelaxin as add-on therapy to SOC versus SOC alone in reducing the number of patients with persistent signs or symptoms of HF / not showing an improvement versus baseline conditions from randomization through Day 5 (persisting need of IV therapy for HF).</p> <p>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.</p> <p>To evaluate the effect of serelaxin as add-on therapy to SOC versus SOC alone in modifying the index length of hospital stay (LOS) by location (e.g., ICU, CCU, cardiology department) in days (and hours for ICU).</p> <p>To evaluate the safety and tolerability of intravenous serelaxin in AHF patients during a period of 30 days following exposure.</p> <p>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.</p>
<b>Study design</b>	This is a multicenter, prospective, open-label, randomized study.



<b>Population</b>	The study population will consist of male and female patients (≥18 years old) admitted to the hospital for AHF, with systolic BP ≥125 mmHg and mild-to-moderate renal impairment.
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Able to provide written informed consent before any study-specific assessment is performed</li> <li>• Male or female ≥ 18 years of age with body weight ≥ 40 Kg and ≤ 160 Kg.</li> <li>• 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)</li> <li>• Admitted/hospitalized for AHF. AHF is defined as including all of the following measured at any time between presentation and the end of screening:             <ul style="list-style-type: none"> <li>• 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)</li> <li>• 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)</li> <li>• BNP ≥500 pg/mL or N-terminal pro b-type natriuretic peptide (NT-proBNP) ≥2,000 pg/mL. For patients treated with valsartan/sacubitril (Entresto®), BNP is not a suitable biomarker and only NT-pro-BNP should be assessed</li> </ul> </li> <li>• 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 hospital including emergency department)]</li> <li>• Received intravenous furosemide of at least 40 mg (or equivalent) at any time between presentation and the start of screening for the study</li> <li>• Impaired renal function defined as an estimated glomerular filtration rate (eGFR) between presentation and randomization defined as ≥25 and ≤75 mL/min/1.73 m<sup>2</sup>, calculated using the simplified Modification of Diet in Renal Disease (sMDRD) equation.</li> </ul>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• 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</li> <li>• 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</li> <li>• Patients with systolic blood pressure &gt;180 mmHg at end of screening or persistent heart rate &gt;130 bpm</li> </ul>

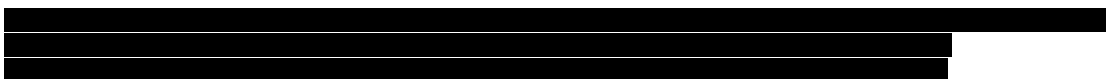


	<ul style="list-style-type: none"> <li>• History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past year</li> <li>• Women of child bearing potential unless they are using highly effective methods of contraception during dosing of study treatment and for 5 days after cessation of study drug or pregnant or nursing (lactating) women</li> <li>• Temperature &gt; 38.5°C (oral or equivalent) or sepsis or active infection requiring IV anti-microbial treatment</li> <li>• Current (within 2 hours prior to randomization) or planned treatment with any IV vasoactive therapies, including vasodilators, positive inotropic agents and vasopressors, 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 systolic BP &gt;150 mmHg at the start of the screening</li> <li>• Significant left ventricular outflow obstruction, uncorrected, such as obstructive hypertrophic cardiomyopathy or severe aortic stenosis (i.e., aortic valve area &lt;1.0 cm<sup>2</sup> or mean gradient &gt;50 mmHg on prior or current echocardiogram), severe aortic regurgitation and severe mitral stenosis</li> <li>• 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)</li> <li>• AHF due to significant arrhythmias, acute myocarditis or hypertrophic obstructive, restrictive, or constrictive cardiomyopathy</li> <li>• Known hepatic impairment or ASL / ALT &gt; 3 ULN</li> <li>• Known presence of active or recurrent bacterial, fungal or viral infection at the time of enrollment</li> </ul>
<p><b>Investigational and reference therapy</b></p>	<p>Serelaxin 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 as add-on therapy to Standard of Care (SOC)/SOC.</p>
<p><b>Efficacy assessments</b></p>	<p>The primary endpoint is time to in-hospital Worsening HF requiring rescue therapy or all-cause death through Day 5.</p> <p>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.</p> <p>The secondary efficacy endpoint is in-hospital Worsening HF requiring rescue therapy as defined above, or all-cause of death or readmission for heart failure through Day 14.</p> <p>Another secondary endpoint in this study is to evaluate 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).</p>



	Moreover, modification of index LOS by location will be evaluated.
<b>Safety assessments</b>	<p>Safety will be assessed by comparing the serelaxin group to the standard of care only group with regard to the frequency of adverse events (AEs) / serious adverse events (SAEs), changes in vital signs, physical examination findings, and clinical laboratory test results (chemistry, hematology and urinalysis).</p> <p>All AEs will be assessed through Day 5</p> <p>All SAEs will be assessed through Day 14 (regardless of causality).</p> <p>Any SAEs experienced after Day 14 should be reported to Novartis only if the investigator suspects a causal relationship to study treatment.</p>
<b>Other assessments</b>	<p>Health related Quality of Life.</p> <p>Healthcare resource utilization.</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
<b>Data analysis</b>	<p>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.</p> <p>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 WHF or death. Subjects without an event will be censored at the earlier of the last assessment or 120 hours after randomization.</p> <p>The primary statistical hypothesis is <math>H_0: \lambda_2/\lambda_1 \geq 1</math> versus the one-sided alternative <math>H_A: \lambda_2/\lambda_1 &lt; 1</math>, where <math>\lambda_1</math> and <math>\lambda_2</math> are the hazard rates for WHF or all cause death in the Standard of Care group and serelaxin group, respectively. The hypothesis will be tested based on the Full Analysis Set (FAS) with a Gehan's generalized Wilcoxon test at a significance level of 0.025 (one-sided).</p> <p>[REDACTED]</p> <p>Time to in-hospital WHF/all cause death/readmission through Day 14 post randomization will be analyzed using survival analysis as in the primary analysis.</p> <p>Treatments will be compared regarding proportions of patients with persistent signs or symptoms of HF/ not showing an improvement vs.</p>

	baseline through Day 5 by means of Chi square test / Fisher Exact test. Index length of stay, overall and by location, in the two treatment groups will be compared using a Wilcoxon rank-sum test.
<b>Key words</b>	Acute Heart Failure, Worsening of Heart Failure, standard of care.



## 1 Introduction

### 1.1 Background

Acute heart failure (AHF) is recognized as a major and escalating public health problem with high disease prevalence associated with poor prognosis. It is the leading medical cause of hospitalization among patients over 65 years of age in the United States, European countries, Australia and New Zealand, with a significant cost burden for the health care systems (McMurray 1998, Fonarow 2008, Roger and Go 2012).

Despite the undoubted clinical importance of AHF, no universally accepted definition exists, but the condition is generally considered to represent the relatively abrupt onset of symptoms and signs secondary to abnormal cardiac function. The cardiac dysfunction can be related to systolic or diastolic myocardial dysfunction, to acute valvular dysfunction, to pericardial tamponade, to abnormalities in cardiac rhythm, or to preload and afterload mismatch. It is a life-threatening condition that requires immediate medical attention, and usually leads to urgent admission to hospital (McMurray et al 2012). In most cases, AHF arises as a result of deterioration in patients with a previous diagnosis of heart failure (HF) (where the term *acute decompensation* is often applied), but it can also occur as the first manifestation of a failing heart (acute *de novo* heart failure) (McMurray et al 2012). AHF should be considered as a heterogeneous set of syndromes, characterized by reduced cardiac output, tissue hypoperfusion and increase in the pulmonary capillary wedge pressure and tissue congestion. Such set of syndromes induce metabolic abnormalities and organ damage, such as renal and liver damage (Metra et al 2010a; Metra et al 2012).

Epidemiological registries and surveys in Europe (Zürich-Helsinki, EFICA, Italian Acute Heart Failure Survey, Euro Heart Survey I and II, British NHS survey) (Rudiger et al. 2005, Zannad et al 2006, Tavazzi et al 2006, Cleland et al 2003, Nieminen et al 2006, Nicol et al 2008), in USA (ADHERE) (Adams et al 2005), in ASIA Pacific region (ATTEND) (Sato et al 2010), and across 9 countries in 4 continents (ALARM-HF) (Follath et al 2011) provided several clues for diagnosis and classification of AHF. These multicenter hospital-based registries and surveys have shown that the typical patient is elderly, with a history of heart failure, coronary artery disease and hypertension. Patient presentation may vary, encompassing worsening congestion, worsening chronic heart failure, pulmonary edema, hypertensive crisis, or cardiogenic shock. Patients typically spend several days in the intensive care unit, with longer admissions in Europe than the United States (Dar and Cowie 2008). The vast majority of patients symptomatically improve during hospitalization; however, their early post-discharge rehospitalization and mortality rates continue to be high (Gheorghide et al 2009, Bueno et al, 2010).

The main clinical challenges in managing AHF patients are to achieve the optimal and sustained resolution of patient congestion aiming for prevention of in-hospital worsening of heart failure (WHF) and organ damage.

The therapeutic approach of AHF has remained the same for decades, being the use of the most acute treatments empirical. Conventional treatment for AHF consists of loop diuretics to reduce fluid overload, plus the addition of nitrates (oral, sublingual or IV) where required to ease vasoconstriction. None of the currently available treatments can demonstrate positive





outcome benefits from randomized clinical trials and, according to the latest ESC-ESH guidelines, treatment in AHF remains largely opinion-based with little good evidence to guide therapy (McMurray et al 2012).

In-hospital worsening of heart failure is considered a clinically relevant end-point in the evaluation of treatment success for AHF (Zannad et al 2013). WHF is defined as a persistence or worsening of symptoms during the acute phase of a heart failure episode requiring intensification of therapy in patients already hospitalized for their acute decompensation (similar to the RELAX-AHF WHF definition). Approximately 10–30% of patients may experience in-hospital WHF in the first few days following hospital admission for AHF (Cotter et al 2010; Weatherley et al 2009).

WHF is a distinct clinical event that represents a severe deterioration of AHF signs/symptoms requiring urgent intervention. Also, it is an event that profoundly alters the patient's disease trajectory. Published data clearly demonstrate that the occurrence of WHF during the hospital phase is associated with a significantly increased risk (2-3 times) of re-hospitalization and mid- and long-term morbidity and mortality outcomes (Cotter et al 2010; Weatherley et al 2009; Zannad et al 2013; Metra 2010; Teerlink et al 2013; Metra 2011; McMurray et al 2007).

Serelaxin is a recombinant form of human relaxin-2, a naturally occurring peptide hormone which is present in both men and women (Dschiertzig et al 2006). The hormone rises to pharmacologic levels during pregnancy, being associated with many of the maternal hemodynamic and reno-vascular adjustments in response to the demands of pregnancy, such as increased cardiac output, increased renal blood flow, and increased arterial compliance (Teichman et al 2010, Du et al 2010, Conrad and Shroff, 2011). More recently, cardiac pleiotropic effects at the tissue level, i.e. contractility increase, angiogenesis, anti-inflammatory, prevention of ischemic-reperfusion injuries and extracellular matrix remodeling have been described.

Serelaxin represents a new pharmacologic class (relaxin peptide family) that is thought to help in AHF by stimulating vasodilation and renal function, boosting cardiac output and decreasing systemic vascular resistance.

Its efficacy and safety in AHF patients has been demonstrated in two studies, the dose-finding phase II study Pre-RELAX-AHF (Teerlink et al 2009) and the phase III pivotal study RELAX-AHF (Teerlink et al 2013, Metra et al 2013). Both the Pre-RELAX-AHF and the RELAX-AHF were randomized, double-blind, placebo-controlled, parallel-group, international trials comparing the intravenous administration of serelaxin for up to 48 hours, started within 16 hours of presentation, added to conventional therapy with placebo in patients hospitalized for AHF with dyspnea, congestion on chest radiography, increased natriuretic peptide levels, mild to moderate renal insufficiency, and systolic blood pressure >125 mmHg.

In the Pre-RELAX-AHF study 234 patients were enrolled, 230 of whom treated with serelaxin at 10, 30, 100 and 250 µg/kg/day or placebo (n=61, 40, 42, 38, 49 patients, respectively). The results showed beneficial effects of serelaxin on both dyspnea and post-discharge clinical outcomes. Serelaxin rapidly improved shortness of breath at 6 hours which was sustained at 12 and 24 hours, with 40% of subjects reporting moderate to marked improvement in the 30 µg/kg/day group, compared with 23% in the placebo group (p=0.044). Similar trends were seen with multiple outcomes including greater weight loss, lower intravenous (IV) loop diuretic use and lower incidence of in-hospital worsening heart failure in the serelaxin groups



(with the 30 µg/kg/day dose group being optimal) compared with placebo. Serelaxin was well tolerated at all doses, the adverse events (AEs) being distributed across study groups without any consistent pattern, the majority of which represented the natural history of patients admitted with AHF.

In the RELAX-AHF study 1161 patients were enrolled, 1138 of whom treated with serelaxin at 30 µg/kg/day or placebo (n=568 and 570 patients, respectively). The results showed a significant relief of dyspnea as measured by change from baseline on a 100-point visual analogue scale (VAS) over 5 days (p=0.0075), even though dyspnea reduction as measured using a 7-point, Likert scale over the first 24 hours (primary end-points) did not achieve statistical significance. The results also showed that, compared with conventional therapy, treatment with serelaxin improved signs and symptoms of patient congestion at Day 2 and significantly reduced WHF episodes through Day 5 and the overall length of index hospital stay, associated with a range of other in-hospital clinical benefits. WHF rates were significantly decreased by serelaxin in RELAX-AHF: significantly fewer patients in the serelaxin group experienced WHF event or death through Day 5 compared with the placebo group (6.5% vs. 12.0%, OR=0.51; 95% CI: 0.33, 0.77; RLX.CHF.003; data on file). Similar results were obtained for WHF through 14 days in placebo group 15.7% (KM) and serelaxin 11.4% (KM), p=0.024 ([Teerlink et al 2013](#)). Serelaxin provided sustained benefits beyond the initial 48 hours of infusion leading to a clinically and statistically significant 37% reduction in the risk of both cardiovascular and all-cause-mortality through Day 180. Serelaxin had favorable effects on the short-term changes in multiple laboratory markers of cardiac, renal, and hepatic damage known to be associated with long-term mortality in AHF. Serelaxin was well tolerated with no notable difference in the overall AE profile; a lower rate of AEs related to renal impairment in the serelaxin treatment arm compared with placebo was noted.

Based on these data, serelaxin represents a new treatment option in AHF, in addition to standard therapy, that may provide rapid and sustained dyspnea relief and improvement of other symptoms and signs of congestion. The findings obtained suggest serelaxin holds promise as the first evidence-based therapy for AHF to substantially improve patients' symptoms and clinical outcomes, including death.

## 1.2 Purpose

This is a multinational, multicenter, prospective, randomized, open label study to confirm and expand the efficacy, safety and tolerability evidence of 48 hours intravenous infusion of serelaxin (30 µg/kg/day) when added to Standard of Care (SOC), in patients admitted to hospital for AHF.

## 2 Study objectives

### 2.1 Primary objective(s)

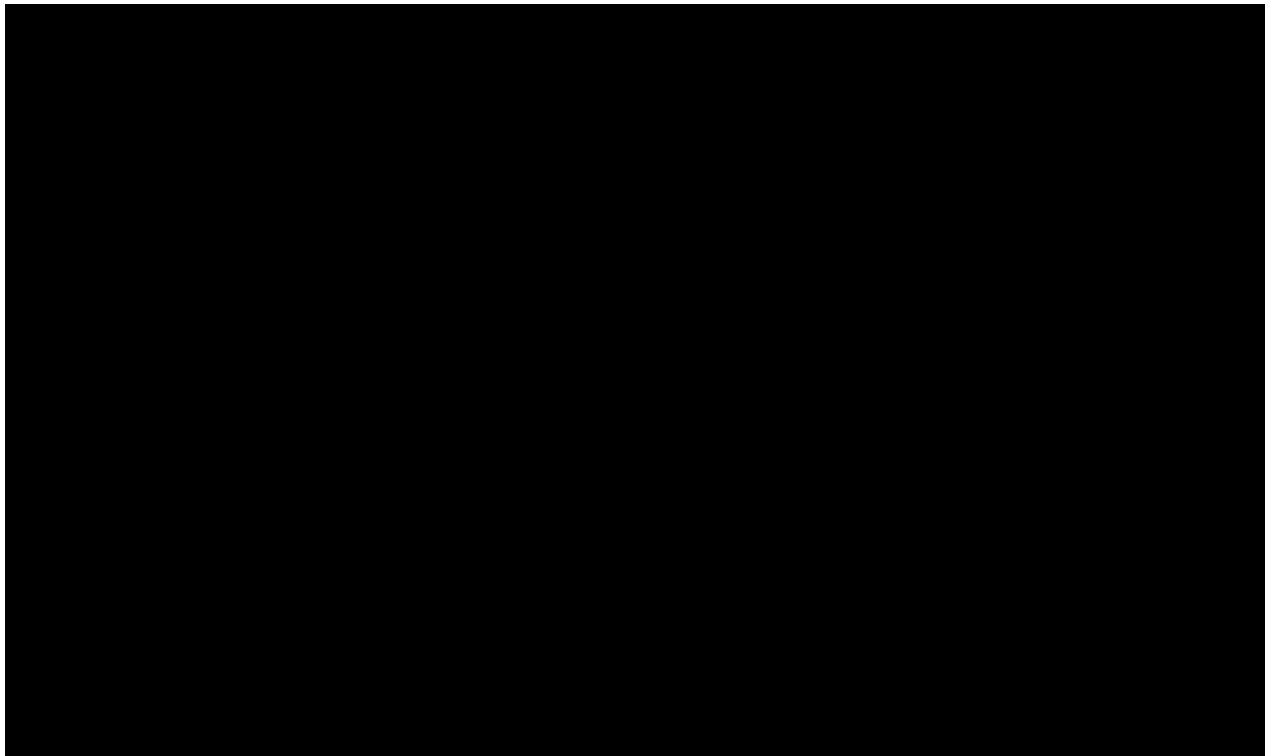
The primary objective of the study is to evaluate the effect of serelaxin as add-on therapy to standard of care (SOC) versus SOC alone in reducing in-hospital worsening HF (WHF) requiring rescue therapy or all-cause death, from randomization through Day 5.



## 2.2 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 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  $\geq 0.3$  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 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.



### 3 Investigational plan

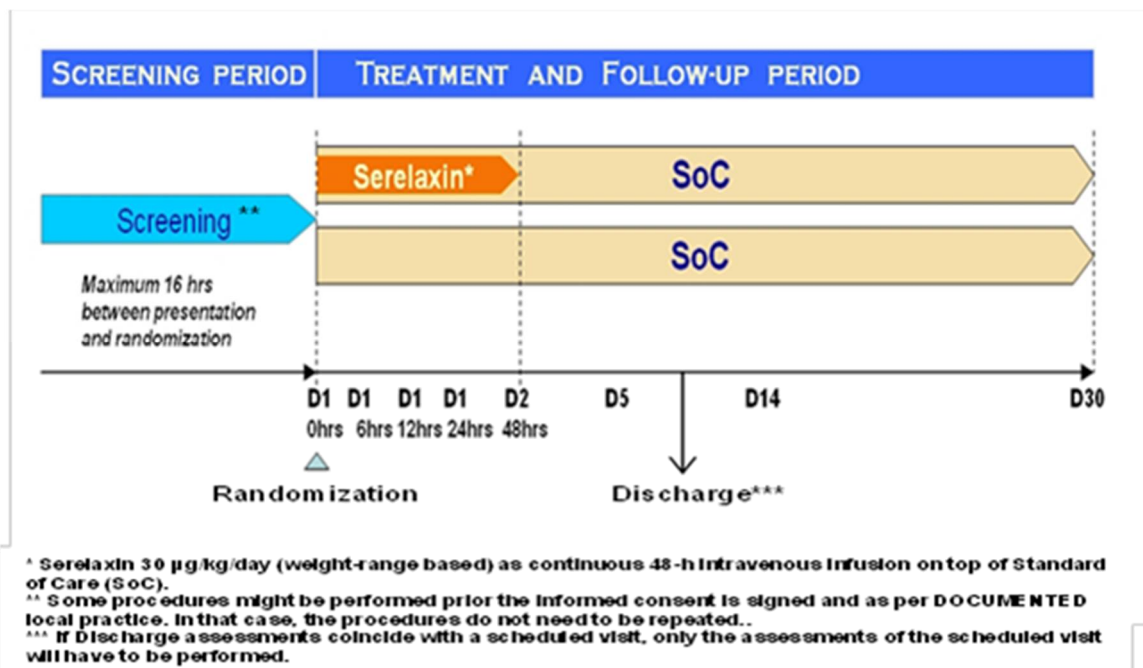
#### 3.1 Study design

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 on the primary composite end-point of in-hospital WHF or all-cause-death through Day 5. The outcome defined as in-hospital WHF (with signs/symptoms of worsening conditions, requiring therapy intensification) will be adjudicated by an Independent Board.

After signing an Ethics Committee or Institutional Review Board approved Informed Consent Form, subjects will be asked to undergo screening procedures for study eligibility. It is essential that screening is completed in time to allow 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 inclusion and none of the exclusion criteria will be 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 (Figure 3-1).

Figure 3-1 Study design



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 previous hospital including emergency department). Investigators will be encouraged to initiate therapy as soon as possible.

Serelaxin drug infusion will be administered via continuous 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 will be monitored regularly during the administration of study drug. If at any time during dosing, the subject's systolic blood pressure is decreased by >40 mmHg from pre-treatment (i.e. just before the study drug infusion) but is  $\geq 100$  mmHg in 2 consecutive measurements 15 minutes apart, serelaxin infusion rate will be decreased by 50% for the remainder of the 48-hour study drug administration. Serelaxin administration will be permanently discontinued at any time if in 2 consecutive measurements, 15 minutes apart, systolic blood pressure is reduced to <100 mmHg. Measures may be taken by the investigator to address the decrease in blood pressure during the intervening 15 minutes, if clinically indicated. Should the study drug dose be decreased or the study drug be discontinued prematurely due to blood pressure decrease, then blood pressure measurements shall be taken every half hour through 2 hours following the blood pressure decrease event, and then hourly through 5 hours after the event onset. Upon completion of the 5-hour post event onset time point, heart rate and blood pressure measurements shall be resumed as outlined in [Section 6.5.2](#). If hypotension persists beyond the 5-hour post event onset, continued hourly blood pressure monitoring should be considered by the investigator, if clinically indicated. Additional blood pressure data collected beyond the 5-hour post event shall be reported in the source documents; only heart rate and blood pressure outlined in [Section 6.5.2](#) will be entered into the case report form (eCRFs).

Patients will be monitored closely during the treatment infusion period (48 hours up to Day 2). The study includes a short-term follow-up through Day 5, discharge and through Day 14. An extension follow-up period up to Day 30, when all subjects will receive a phone call to ascertain vital status and the need for repeated hospitalization.

Patients will undergo clinical evaluations including AHF symptom assessments, vital signs, physical examination emphasizing signs of HF, as well as the need for further IV or oral HF treatment and the occurrence of worsening HF events at least daily while hospitalized and then at Day 14. Subjects randomized to either serelaxin arm or SOC, and discharged prior to Day 5 will be required to return to the hospital/clinic for scheduled visits at Days 5 and 14. Should the patient not be able to come for the scheduled visit at Day 14, every effort should be made to contact the patient via phone to obtain essential vital details (See [Table 6-1](#)).

Safety will be assessed by monitoring AEs and vital signs and performing physical examinations and routine clinical laboratory tests as per protocol, as well as tests felt to be clinically indicated by the investigator up to Day 30.

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and through Day 14 must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after Day 14 should be reported to Novartis only if the investigator suspects a causal relationship to study treatment.

Patients are required to receive standard of care treatment for HF during both the index hospitalization and post-discharge per local and institution practice guidelines.

[REDACTED]

[REDACTED]

## 3.2 Rationale of study design

### Choice of open-label design

The open label (OL), randomized design was chosen after careful considerations and the possibility of a double blind (DB) design had been evaluated. The DB could have brought both benefits and challenges, the benefits based on a high credibility of the study results in the academic community (internal validity), while the challenges would have been operational and would have had an impact on complexity and recruitment speed.

The choice of a randomized OL design will offer a different balance of benefits, with emphasis on external validity ([Juni et al., 2001](#)), as literature supports randomization in an OL design as a sensible option when DB is not chosen ([Casteels et al., 2007](#)).

The aim of the RELAX-AHF-EU study is to generate evidence in the management of AHF in real-life settings that will complement existing and future serelaxin data sets based on DB-RCT (double-blind randomized controlled trials) in AHF.

Decision makers in Health Care are indeed increasingly interested in using high-quality scientific evidence to support clinical and health policy choices, and they welcome practical (or pragmatic) clinical trials ([Tunis et al., 2003](#)).

These practical clinical trials are characterized by the 1) selection of clinically relevant alternative interventions to compare, 2) inclusion of a diverse population of study participants, 3) recruitment of participants from heterogeneous practice settings, and 4) collection of data on a broad range of health outcomes.

The OL randomized controlled design of RELAX-AHF-EU will better reflect the way physicians really manage patients. A variety of different hospital settings will participate (cardiology departments, internal medicine wards, and emergency units) from a large selection of countries.

The OL nature of the study also creates an opportunity to reach out to a variety of clinical institutions and structures, closely reflecting real-life clinical contexts.

To note that the primary endpoint, which contains elements of subjectivity, will be adjudicated in a blind way by a committee of experts (Adjudication Committee) appointed by the study Executive Committee.

### **3.3 Rationale of dose/regimen, route of administration and duration of treatment**

Previous results in the Phase II Pre-RELAX-AHF (a dose finding trial) and in Phase III RELAX-AHF support the selection of serelaxin 30 µg/kg/day as the dose to be used via intravenous infusion for 48 hours.

In the RELAX-AHF study, serelaxin treatment significantly improved early signs and symptoms of congestion, reduced WHF through Day 5 and the length of index hospital stay in addition to a range of other in-hospital clinical benefits; it also demonstrated overall good safety and tolerability. The favorable efficacy and safety observed in the RELAX-AHF study support the adoption of the same dosing regimen of serelaxin administration in this study.

For patients who experience significant systolic blood pressure decrease during the 48-h serelaxin infusion, protocol-specified dosing adjustments and/or discontinuations rules must be followed to ensure patient safety (refer details in [Section 3.1](#) and [Section 5.5.5](#)).

### **3.4 Rationale for choice of comparator**

There is no evidence based therapy for the treatment of AHF and thus an active comparator is not available. All patients in this study will be required to receive standard of care HF management during the study.

### **3.5 Purpose and timing of interim analyses/design adaptations**

Not applicable.

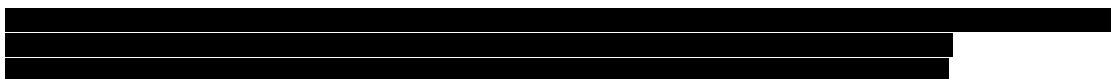
### **3.6 Risks and benefits**

The management of AHF remains an area of unmet medical need, even though, therapies are available to improve AHF-related symptoms, no evidence based therapy for the treatment of AHF is currently available.

Previous studies with serelaxin ([Teerlink et al., 2011 and 2013](#)) showed significant improvement in dyspnea and signs and symptoms of congestion, and demonstrated an association of the drug with significant reductions in early worsening heart failure events and length of stay during the index hospitalization, including duration of intensive care. Moreover, pre-specified biomarker changes in previous studies suggest serelaxin therapy has a protective effect on both the heart and kidney.

Serelaxin was generally well tolerated with no notable differences in the overall adverse event profile compared to placebo. Although a decrease in blood pressure can occur due to the vascular mechanism of action of the drug, worse outcomes were not observed. In order to ensure patient safety, the protocol provides instructions for the management of systolic blood pressure (SBP), including close and careful monitoring as well as mandatory dose adjustment or stopping rules.

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria and close clinical monitoring. Since the potential of immunogenicity as a result of repeated intravenous dosing has not yet been fully characterized, those patients who participated in prior serelaxin clinical studies will be excluded. It is also important to note that all patients in



this study will be required to receive standard of care background HF management during hospitalization as well as the period of 30 days following exposure.

Refer to the Investigator's Brochure (IB) for additional information regarding the safety profile of serelaxin.

## 4 Population

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

The study plans to randomize approximately 3183 patients in approximately 600 study centers mainly in Europe.

### 4.1 Inclusion criteria

Subjects must fulfill **all** of the following criteria at screening to be eligible for the study. The screening period is defined as that 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 diagnostic 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  $\geq$ 18 years of age with body weight  $\geq$  40 Kg and  $\leq$  160 Kg.
3. Systolic blood pressure  $\geq$ 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:
  - a. 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)
  - b. 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)
  - c. N-terminal pro B-type natriuretic peptide (NT-proBNP)  $\geq$ 2,000 pg/mL or BNP  $\geq$ 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  $\geq 25$  and  $\leq 75$  mL/min/1.73 m<sup>2</sup>, calculated using the simplified Modification of Diet in Renal Disease (sMDRD) equation (Levey AS et al., 2007; Myers GL et al., 2006).

## 4.2 Exclusion criteria

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this 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.

1. 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.
2. 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.
3. Patients with systolic blood pressure >180 mmHg at the end of screening or persistent heart rate >130 bpm
4. Temperature >38.5°C (oral or equivalent) or sepsis or active infection requiring IV anti-microbial treatment.
5. 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  $\leq 0.1$  mg/kg/hour if the patient has a systolic BP >150 mmHg at the start of the screening.
6. Significant left ventricular outflow obstruction, uncorrected, such as obstructive hypertrophic cardiomyopathy or severe aortic stenosis (i.e., aortic valve area <1.0 cm<sup>2</sup> or mean gradient >50 mmHg on prior or current echocardiogram), severe aortic regurgitation and severe mitral stenosis.
7. 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).
8. 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.

9. Women of childbearing 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 suppositoryIn 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 childbearing potential.
10. 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.
11. Acute myocarditis or hypertrophic obstructive, restrictive, or constrictive cardiomyopathy (does not include restrictive mitral filling patterns seen on Doppler echocardiographic assessments of diastolic function).
12. Major surgery, including implantable devices (e.g. ICD, CRT), or major neurologic event including cerebrovascular events, within 60 days prior to screening.
13. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past year.



14. Hematocrit <25% or a history of blood transfusion within the 14 days prior to screening or active, life-threatening GI bleeding.
15. Known hepatic impairment or AST / ALT > 3 ULN.
16. Known presence of active or recurrent bacterial, fungal or viral infection at the time of enrollment.
17. 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.
18. 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, behavioral or cognitive disorders, sufficient to interfere with the patient's ability to comply with the protocol instructions or follow-up procedures.
19. 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.
20. Inability to follow instructions or comply with follow-up procedures.
21. Known hypersensitivity to serelaxin or similar substances or to any of the excipients.

## **5 Treatment**

### **5.1 Protocol requested treatment**

#### **5.1.1 Investigational treatment**

Serelaxin will be administered according to a weight-range adjusted dosing regimen at a nominal dose of 30 µg/kg/day (refer to the details in [Section 5.5.4](#)), 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 will 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*.

#### **5.1.2 Additional study treatment**

No additional treatment beyond investigational treatment is requested for this trial. Nevertheless, all randomized patients will be required to receive standard of care background HF management during both the index hospitalization and post discharge, according to local guidelines/international standards. This treatment post-randomization 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.



## 5.2 Treatment arms

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

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

## 5.3 Treatment assignment, randomization

At baseline, all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify 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 will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. A patient randomization list will be 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 will be 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.

The randomization scheme for patients will be reviewed and approved by the Randomization Office.

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, where 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.

## 5.4 Treatment blinding

Treatment code will be open to patients, investigator staff, and persons performing the assessments. The clinical trial team (e.g. Clinical Trial Lead, Clinical trial Manager, Medical Lead, Trial Statistician) will be blinded to the identity of the treatment from the time of randomization until database lock. Randomization data will be kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the exception of those mentioned in the Safety Manual.



## **5.5 Treating the patient**

### **5.5.1 Patient numbering**

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 investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The assigned patient number should be entered in the field labeled “Subject ID” on the electronic Case Report Form (eCRF) data entry screen.

If a patient correctly randomized fails to be treated for any reason, the IRT must be notified immediately that the patient was not treated. The patient will be followed up to Day 30 and relevant information, together with the reason for not being treated, will be entered into the eCRF.

### **5.5.2 Dispensing the investigational treatment**

Each study site will be supplied by Novartis with investigational treatment in kits containing 1 vial of serelaxin each, enough study drug for 24 hours of 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 patients randomized to serelaxin only).

The investigational treatment packaging has a 2-part label. Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient’s unique subject number.

### **5.5.3 Handling of study treatment**

#### **5.5.3.1 Handling of investigational treatment**

Investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all investigational treatment shall be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the investigational treatment but no information about the patient except for the patient number. The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational treatment, packaging, drug labels and a copy



of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

### 5.5.3.2 Handling of other study treatment

Patients will receive standard of care as per local clinical practice. The investigator will enter information on standard of care provided to the patient in the eCRF.

### 5.5.4 Instructions for prescribing and taking study treatment

Serelaxin drug infusion will begin as soon as possible after randomization, but not later than 4 hours after start of study drug preparation, and will be administered via continuous IV infusion for 48 hours.

Serelaxin infusion solution must be prepared in infusion bags containing 5% dextrose as a diluent. Recommended infusion bags, which have been tested and qualified for use with serelaxin, are detailed in the *Pharmacy Manual*. However, there is no restriction of use of any other 250 mL infusion bag with 5% dextrose.

Compatible infusion filters which have been tested and qualified for use with serelaxin, must be used to administer the study drug and are detailed in the *Pharmacy Manual*.

For each randomized patient to receive the study drug according to a weight-range adjusted dosing regimen over a period of 24 hours ([Table 5-1](#)), the required amount of study drug will be withdrawn from the 6-mL vials (with stopper and crimp caps with 3.5 mL fill) contained in the kits, injected into a 250 mL intravenous bag of 5% dextrose solution recommended above and then infused at a constant rate of 10 mL/hour [via an infusion pump, a drip or any other controllable system for Germany only]. Details of study drug preparation and infusion can be found in the *Pharmacy Manual*.

Study drug will be dispensed only by study staff qualified to perform that function under applicable local laws and regulations for the study site(s), according to the protocol and Schedule of Events (see [Table 6-1](#)).

Patients who do not meet any criteria for interruption after 24 hours of infusion and are therefore eligible to continue with other 24 hours of study drug infusion will be required to receive study drug prepared from a second kit or pair of kits also assigned via IRT, depending on the patient's body weight.

The study drug kits, allocated to each randomized patient via IRT, containing one 6-mL vial of serelaxin (with 3.5 mL fill), will be used to compound study drug for the first 24 hours of infusion for all patients <115 kg in weight; in cases when the subject is  $\geq 115$  kg, two study drug kits will be assigned via IRT for the first 24 hours of infusion. The body weight determined between presentation and randomization, rounded up to the nearest 0.5 kg, will be used for the calculation of the dose for each patient, for the entire 48-hour infusion period. Study drug from a second kit or pair of kits, also assigned via IRT depending on the patient's body weight as assessed between presentation and randomization, will be used to continue the infusion for the second 24 hours. The second study drug kit should be obtained by calling IRT close to the end of the 1st 24 hours of study drug infusion.



**Table 5-1 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.

### 5.5.5 Permitted dose adjustments and interruptions of study treatment

Systolic Blood Pressure (SBP) has to be  $\geq 125$  mmHg for the patient to be eligible, and then  $\geq 125$  mmHg during the screening period, in particular at the end of the screening period just before calling the IRT for randomization. In many centers, continuous cardiac monitoring will probably be applied and this will keep the site informed about SBP values.

Considering the high fluctuation of blood pressure in patients with decompensated HF, especially because the patient might be under the effect of nitrates (even at low dose) and diuretics, it is advised to minimize the time windows between the end of screening, the IRT call and start of the serelaxin infusion.

In practice:

- BP has to be measured at the end of screening and SBP must be  $\geq 125$  mmHg before calling the IRT. Once the patient is randomized, the study drug should be prepared promptly (if the patient is in the serelaxin group).
- Just before the immediate start of study drug infusion, SBP must be assessed again. During that interval between randomization and infusion start, sometime will elapse (30 to 60 minutes in most cases) and BP may fluctuate.
  - It is not required that pre-infusion SBP be  $\geq 125$  mmHg (SBP  $\geq 125$  mmHg is an inclusion criterion and matters only up to randomization)
  - If at the immediate start of study drug infusion, SBP is below 100 mmHg (SBP  $< 100$  mmHg), serelaxin should not be started, neither now nor later. The patient will remain in the study up to 30 days but will not have received serelaxin
  - If a blood pressure fall has occurred since randomization but SBP is still  $\geq 100$  mmHg, the decision to start or not the infusion remains at the discretion of the investigator, based on the hemodynamic context of the patient (i.e. previous hemodynamic stability, DBP, concomitant medications, medical response to IV furosemide/diuretics, etc.).

Of note, there is no mandatory time window between randomization and start of the study drug infusion. This time span should be kept as short as possible. For microbiological reasons, there is a maximum time of 4 hours allowed between preparation (mixing) of the study drug and infusion start.

If at any time during the study drug infusion, the subject's systolic blood pressure decreases by  $>40$  mm Hg from just before the study drug infusion but is  $\geq 100$  mmHg in two consecutive measurements 15 min apart, the serelaxin infusion rate will be decreased by 50% for the



remainder of the 48-hour study drug administration. Serelaxin administration will be permanently discontinued at any time if in 2 consecutive measurements; 15 minutes apart, systolic blood pressure is reduced to <100 mmHg.

Table 5-2 describes the actions required for a systolic BP decrease during the period of study drug infusion, which must be strictly followed.

**Table 5-2 Dosing adjustment of study drug administration in the event of systolic BP decrease through completion of study drug infusion**

Changes in systolic BP during infusion*	Adjustments of study drug administration
Decrease >40 mmHg from pre-treatment (i.e., measured just before the immediate start of study drug infusion), but systolic BP remains ≥ 100 mmHg	Reduce the infusion rate by half for the remainder of the study drug administration, i.e., reduce infusion rate from 10 mL/hour to 5 mL/hour for the remainder of 48-hour infusion
Decrease in absolute value of systolic BP to <100 mmHg	Permanently terminate study drug infusion

\* These systolic BP values should be confirmed by two measurements taken 15 minutes apart.

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 AEs suspected to be related to study drug. If dosing is discontinued for BP decreases, or any safety reasons, it should not be restarted. Re-administration of study drug once terminated for safety reasons is not allowed. The total time from initiation of study drug infusion to completion must not exceed 48 hours. In the event that study drug administration is discontinued, regardless of the reason, the patient will continue to be followed at all study visits defined in the protocol. These changes in study drug dose must be recorded on the Dosage Administration Record eCRF.

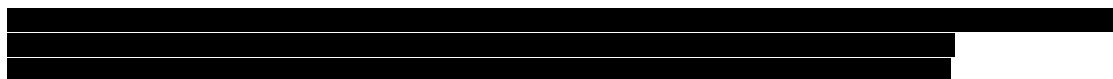
### 5.5.6 Rescue medication

The investigator may prescribe any medications and/or supportive care during the study based on clinical needs. Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies in the eCRF.

### 5.5.7 Concomitant treatment

To be eligible for the study, all patients must have received IV furosemide of at least 40 mg (or equivalent e.g. Torasemide 20 mg or Bumetanide 2 mg) at any time between presentation and the start of screening for the study. This total 40 mg IV furosemide or equivalent loop diuretic dose might include the dose that the patient has received in the emergency service ambulances.

Patients will not be enrolled in the study if concomitant therapy for AHF includes current (within 2 hours prior to randomization) or planned (through the completion of study drug infusion) treatment with any cardiovascular IV 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), with the exception of IV nitrates at a dose of  $\leq 0.1$  mg/kg/hour if the patient has a systolic BP  $>150$  mmHg at the start of the screening. Use of IV furosemide (at least 40 mg or equivalent) is an inclusion criterion. Further doses of IV or oral furosemide can be administered at any time after enrollment.

The investigator may prescribe any additional medications during the study as made necessary by the patients' condition. Administration of any standard AHF treatment shall in no instance be delayed or withheld due to patient's participation in the study. Standard AHF treatment includes, but is not limited to, administration of the major classes of cardiovascular medications, as well as administration of oxygen, analgesics, anxiolytics and sedatives, as needed.

Heart failure medications, procedures and significant non-drug therapies administered after the patient was enrolled into the study must be recorded. The investigator shall instruct the patient to notify the investigator or associated study personnel about any new medications he/she takes after discharge and up to Day 30.

Administration of any cardiovascular IV therapies, including vasodilators (including nesiritide), positive inotropic agents and vasopressors, or mechanical support (intra-aortic balloon pump, endotracheal intubation, assisted ventilation (invasive or non-invasive), or any ventricular assist device), is allowed when necessary in both groups. However, in the serelaxin group caution should be exercised and potential additive hypotensive effects be discussed, in order to decide whether to maintain or discontinue the serelaxin infusion during administration of the above mentioned additional AHF drugs or procedures.

Any concomitant treatment taken by a subject during the hospital stay and until Day 30 will be recorded.

### **5.5.8 Prohibited Treatment**

Use of IV vasoactive therapies within 2 hours prior to randomization is an exclusion criterion with the exception of IV loop diuretics, or IV nitrates at a dose of  $\leq 0.1$  mg/kg/hour if the patient has a systolic BP  $>150$  mmHg at the start of the screening. Thus, study drug shall be started concomitantly with IV nitrates only if at a low dose ( $\leq 0.1$  mg/kg/hour) in a patient with high systolic BP ( $>150$  mmHg).

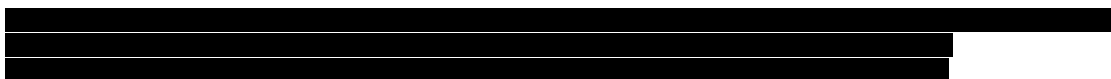
Post-randomization, the investigator may prescribe any additional medication as made necessary by the patients' condition. Administration of any standard AHF treatment shall never be delayed or withheld due to patient's participation in the study.

The investigator shall exercise caution when up-titrating or adding concomitant standard AHF therapies that might decrease BP during study drug infusion. Investigator may consider not administering all blood pressure (BP) lowering medication simultaneously. Changes to these medications during the index hospitalization shall be recorded on the eCRF.

### **5.5.9 Discontinuation of study treatment**

The investigator shall discontinue the study drug infusion for a patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

In particular, the study drug administration must be discontinued under the following circumstances:



- The patient's systolic BP falls to <100 mmHg in two consecutive measurements 15 min apart. Measures may be taken by the investigator to address the decrease in blood pressure during the intervening 15 minutes, if clinically indicated
- Pregnancy
- Any other protocol deviation that results in significant risk to the patient's safety

During the study drug infusion, administration of any cardiovascular IV therapies, including vasodilators (including nesiritide), positive inotropic agents and vasopressors, or mechanical support (intra-aortic balloon pump, endotracheal intubation, assisted ventilation, or any ventricular assist device) is allowed. The continuation or discontinuation of study drug infusion will then be at the discretion of the investigator.

Of note, patients who discontinue investigational treatment shall NOT be considered withdrawn from the study, and are required to be followed per the visit/assessment schedules illustrated in [Table 6-1](#) until the study is complete. The investigator must register the patient's discontinuation from the study and/or investigational treatment in the eCRF.

Patients can also refuse to participate in specific aspects of the study and/or take study medication at any time without withdrawing consent. Investigators shall make every effort to accommodate the needs of the patients to make it possible for them to continue to participate in the remaining aspects of the study. This includes performing telephone visits to obtain vital status and/mortality information for patients who are unable to or refuse to return for clinic visits.

#### **5.5.10 Withdrawal of consent**

Patients may voluntarily withdraw from the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study anymore and does not want any further visits or assessments and does not want any further study related contacts and does not allow analysis of already obtained biologic material.

If a patient withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

#### **5.5.11 Loss to follow-up**

The investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. to collect safety information, the vital status and hospitalizations at 30 days.

#### **5.5.12 Emergency breaking of assigned treatment code**

Not applicable.



### **5.5.13 Study completion and post-study treatment**

After randomization, patients will be followed up through Day 5 and 14 and then at Day 30. The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

Any SAEs experienced after Day 14 should be reported to Novartis only if the investigator suspects a causal relationship to study treatment.

### **5.5.14 Early study termination**

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient shall be seen as soon as possible and treated as a prematurely withdrawn patient. The Executive Committee can also stop the study based on DMC recommendation; the final decision is up to Novartis. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing Institutional review boards (IRBs) and/or Ethics Committees (ECs) of the early termination of the trial.

## **6 Visit schedule and assessments**

[Table 6-1](#) lists all of the assessments and an “x” indicates 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 their survival status.

Patients who prematurely discontinue the investigational treatment remain in the study and shall undergo all the assessments illustrated in [Table 6-1](#).

If a patient withdraws from participation in the study, 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 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 <sup>12</sup>	Discharge <sup>13</sup>	D14 (± 2)	D30 (± 2)
Phase			Drug Infusion <sup>0</sup>				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 <sup>1</sup>	X		X	X	X	X	X	X	X	X	X	
Height	X											
Body weight measurement <sup>1</sup>	X				X	X	X	X	X	X	X	
Physician assessment of signs and symptoms of HF <sup>1</sup>		X	X	X	X	X	X	X	X	X	X	
Worsening Heart Failure (WHF) <sup>2</sup>			X	X	X	X	X	X	X	X	X	
ECG	X								X	X		
Chest X-Ray <sup>3</sup>	X											
BP and HR measurements <sup>4</sup>	X	X	X	X	X	X	X	X	X	X	X	
NT-pro-BNP or BNP for study entry <sup>5</sup>	X											
Serum cTnT or cTnI <sup>6</sup> for study entry	X											
Pregnancy test <sup>6</sup>	X											
eGFR (sMDRD) <sup>6</sup>	X					X			X	X		
Laboratory tests (Local Laboratory) <sup>6,7</sup>	X				X	X			X	X	X	
		X				X			X			
		X				X			X			
		X			X	X			X			
		X				X			X			
HRQoL questionnaire		X				X			X	X	X	



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 <sup>12</sup>	Discharge <sup>13</sup>	D14 (± 2)	D30 (± 2)
Phase			Drug Infusion <sup>0</sup>				Post-treatment daily assessment				Follow-up	
(EQ-5D-5L)												
Healthcare Resource Utilisation <sup>9</sup>		X	X	X	X	X	X	X	X	X	X	X
Contact IRT <sup>10</sup>	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 <sup>11</sup>	X	X	X	X	X	X	X	X	X	X		
Serious Adverse Events <sup>11</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Vital Status									X	X	X	X

<sup>0</sup> 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.

<sup>1</sup>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](#).

<sup>2</sup>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.

<sup>3</sup>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.

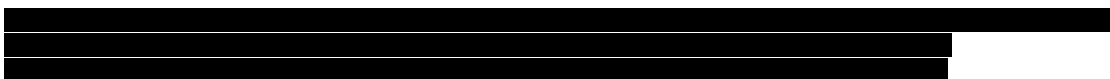
<sup>4</sup>BP and HR measurements should be performed for all patients at the beginning of the screening period (after ICF signature) and at the end of the screening period (prior to randomization). For serelaxin patients, frequent BP and HR measurements should be performed between randomization and 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 timepoints. 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.

<sup>5</sup> 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. When a patient treated with valsartan/sacubitril (Entresto®) is considered for randomization into the trial, only NT-proBNP and not BNP should be assessed during the screening phase. BNP is not a suitable biomarker of heart failure in patients treated with Entresto® because BNP is a neprilysin substrate. NT-proBNP is not a neprilysin substrate and is therefore a more suitable biomarker.

<sup>6</sup> 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.

<sup>7</sup> 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.

<sup>9</sup> 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.



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 <sup>12</sup>	Discharge <sup>13</sup>	D14 (± 2)	D30 (± 2)
Phase			Drug Infusion <sup>0</sup>				Post-treatment daily assessment				Follow-up	

<sup>10</sup> 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.

<sup>11</sup> 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.

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

<sup>13</sup> 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.



## 6.1 Information to be collected on screening failures

All patients who have signed informed consent but are not entered into the next epoch (study phase) will have the study completion page for the screening epoch, demographics, inclusion/exclusion, and SAE data collected. AEs that are not SAEs will be followed by the investigator and collected only in the source data.

All patients who have signed informed consent and are entered into the next epoch of the study will have all AEs **occurring after informed consent is signed** recorded on the Adverse Event eCRF.

Investigators will have the discretion to record abnormal test findings on the medical history eCRF whenever, in their judgment, the test abnormality occurred prior to the informed consent signature.

## 6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include date of birth, age, sex, race, ethnicity, education level, living arrangement, weight and height, relevant medical history/current medical condition present before signing informed consent. If patient body weight cannot be measured at screening because of the patient's physical condition, a verbal weight will be acceptable (weight should be obtained as soon as the patient is physically able to). Where possible, diagnoses and not symptoms will be recorded.

Baseline HF medications and other CV medications will be recorded in eCRFs separately from other medications. Likewise, detailed HF history and other relevant CV medical history will be recorded on eCRFs separately from other medical history.

Chest X-Ray will not be considered a study related procedure and shall be performed according to local clinical practice. Pulmonary congestion should be present upon clinical assessment and chest X-Ray as per local clinical 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.



Physical examination, assessment of signs and symptoms of HF and its worsening will be also performed. Relevant documentation shall be filed in the patient's medical record and available information entered in the eCRF.

The eGFR to determine eligibility of the patient for screening into the trial will be calculated at screening from the serum creatinine concentration measured locally.

Serum cTnT or cTnI and NT-proBNP or BNP will be performed only at screening by local laboratory (cTnT or cTnI). Values prior to the screening but performed within the index hospitalization can be used. NT-proBNP assessed specifically by point of care device is only required if the site is not able to obtain local lab test results within the 16-hour timeframe or if local lab does not offer NT-pro BNP or BNP at all.

At screening, a locally-analyzed urine/serum pregnancy test (according to the local practice) will be performed for all females of childbearing potential. Any subject with a positive pregnancy test at Screening will be excluded from the study.

Baseline information on healthcare resource utilization (HRU) and HRQoL will be collected also.

### **6.3 Treatment exposure and compliance**

Information on study drug administration, infusion time and rates and possible discontinuation of intravenous infusion will be reported in the eCRF.

Study drug accountability will also be verified by the site monitor while performing routine site visits and at the completion of the study.

### **6.4 Efficacy**

#### **6.4.1 In-hospital Worsening Heart Failure/all-cause death through Day 5**

The primary endpoint is time to in-hospital Worsening Heart Failure (WHF) requiring rescue therapy or all-cause death through Day 5.

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 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.

Relevant evaluations will be 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 will be performed at 6, 12, 24 and 48 hours from randomization, daily through index hospitalization, at Day 5 and discharge, and then at Day 14.



#### **6.4.1.1 Assessment of signs and symptoms of heart failure**

The investigator or appropriate qualified designee will evaluate 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 will be 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 serelaxin arm. For patients in the SOC arm, relevant evaluations will be 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.

For details of assessment see [Appendix 3](#).

#### **6.4.2 In-hospital Worsening Heart Failure/all-cause death through Day 14**

The secondary efficacy endpoint is Time to Worsening HF requiring rescue therapy as defined above, or death or readmission for heart failure through Day 14.

In this study we are also collecting information on 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).

#### **6.4.3 Index Length of hospital stay**

Changes in index length of hospital stay and per location (emergency ward, emergency care unit, etc.) will be evaluated by treatment group.

#### **6.4.4 Appropriateness of efficacy assessments**

The efficacy assessments selected are standard for this indication/patient population. In-hospital WHF is a clinically meaningful efficacy variable that gives the investigator an indication of the evolution of the clinical condition of the patients as well as information on treatment efficacy. Mortality in AHF patients remains high despite contemporary standard-of-care HF management, and all-cause death is a robust and established efficacy endpoint to assess the effect of pharmacologic interventions on clinical outcomes of HF patients. The various assessments planned during the in-hospital phase, as well as at 14 and 30 days follow-up, will provide useful and complementary information on serelaxin efficacy in acute HF patients.

### **6.5 Safety**

Safety will be assessed by comparing the serelaxin group to the standard of care only group with regard to the frequency of AEs/SAEs, changes in vital signs, physical examination findings, and clinical laboratory test results (chemistry, hematology, and urinalysis). All non-serious AEs will be collected through Day 5 and SAEs (regardless of causality) through Day 14. Any SAEs experienced after Day 14 should be reported to Novartis only if the investigator suspects a causal relationship to study treatment.





### **6.5.1 Physical examination**

An overall physical examination will be 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 examination. An abbreviated physical examination will be performed at 6, 12, 24 and 48 hours after start of study drug infusion in the serelaxin arm and daily through index hospitalization, at Day 5, at discharge and then Day 14, and includes the examination of general appearance and vital signs (SBP/DBP and pulse). For patients in the SOC arm, an abbreviated physical examination will be performed at 6, 12, 24 and 48 hours from randomization, 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 a non-serious AE, must be recorded on the Adverse Event section of the eCRF ([Section 7.1](#)). Significant findings after signing the informed consent, up to and including Day 14, which meet the definition of a SAE, must be recorded on the Serious Adverse Event section of the eCRF ([Section 7.2](#)), 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 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.

### **6.5.2 Vital signs**

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

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 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, BP and heart rate (HR) measurements will be 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 be also performed at 6, 12, 24, 48 hours, 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 timepoint.

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 the systolic blood pressure measured just before the start of study drug infusion but is  $\geq 100$  mmHg in two consecutive measurements 15 min apart, serelaxin infusion rate will be decreased by 50% for the remainder of the 48 hour study drug administration. Serelaxin administration will be permanently discontinued at any time if in two consecutive measurements 15 minutes apart, systolic blood pressure is reduced to  $<100$  mmHg (also see details in [Section 5.5.5](#)).

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.

### 6.5.3 Height and weight

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

Body weight (to the nearest 0.1 kilogram [kg] or 0.1 pounds [lbs] in indoor clothing, but without shoes) will be measured at Screening and at 24 and 48 hours after study drug infusion in serelaxin arm, and daily through index hospitalization, at discharge, and at Day 5 and then at Day 14. For the SOC patients, body weight will be measured at screening, 24 and 48 hours after randomization and daily through index hospitalization, at discharge, and at Day 5, 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 will be acceptable. Height/weight measurements shall be obtained as soon as the patient is physically able.

### 6.5.4 Laboratory evaluations

All screening, baseline and post-baseline specimens

will be analyzed by the 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 day.

Laboratory values that exceed the boundaries of a notable laboratory abnormality should be assessed for AEs and additional evaluations should be performed, as judged appropriate by the investigator. If the laboratory abnormality induces clinical signs and symptoms or requires therapeutic intervention, then the diagnosis or medical condition must be entered on the AE screen of the patient's eCRF. If the laboratory abnormality is the primary reason for an unforeseen hospitalization or otherwise fulfills the seriousness category of an AE, then the procedure for immediate notification of SAEs must be followed. Likewise, if the laboratory abnormality leads to discontinuation from the study, then the patient must be followed until the abnormality resolves or is judged to be permanent.

Clinical laboratory tests including hematology and chemistry will be performed locally at screening, at 24 and 48 hours, at Day 5, at discharge and then Day 14 (in both arms). The tests done at each visit are standard medical tests. A total of approximately 10 mL will be collected when each blood sample is taken.

Urinalysis will be conducted at baseline, 24 and 48 hours only and analyzed locally.

In those sites in which markers of cardiac injury or stress are measured as per local practice the values should be entered into the eCRF ONLY in the context of a WHF event.

#### **6.5.4.1 Hematology**

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

#### **6.5.4.2 Clinical chemistry**

Serum chemistry evaluations will 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 and total protein. In addition, hemoglobinA1c will be measured at screening only. For Liver Events only, fractionated bilirubin, which includes testing for total bilirubin, direct bilirubin, and indirect bilirubin, should be performed in accordance with [Table 14-2](#).

#### **6.5.4.3 Urinalysis**

Urinalysis will include measurement of glucose, ketones, pH, protein and specific gravity. The analysis will be performed according to local lab methods /procedures.

#### **6.5.5 Electrocardiogram (ECG)**

ECGs will be performed and interpreted locally at screening and at Day 5 and at discharge. The ECG interpretation and the person interpreting the ECG must be recorded in the source documents.

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.



Single 12 lead ECGs are collected. The original ECGs on non-heat-sensitive paper or a certified copy on non-heat sensitive paper, appropriately signed, should be collected and archived at the study site.

Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding. Clinically significant ECG findings prior to dosing with investigational treatment must be discussed with the sponsor.

Clinically significant abnormalities should be recorded on the relevant section of the medical history/Current medical conditions/AE eCRF page as appropriate.

### 6.5.6 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

### 6.6 Other assessments

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

#### 6.6.4 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

[REDACTED]

this study the first administration of the EQ-5D-5L questionnaire will occur 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: first one asking the patient to retrospectively describe how he/she felt on the day of admission, and 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 will be completed by all study patients (both serelaxin and SOC groups) at baseline, at Day 2, at Day 5, at discharge and Day 14.

Completed questionnaires will be reviewed by the investigator before the clinical examination for responses that may indicate potential AEs or SAEs. The investigator shall review not only the responses to the questions in the questionnaires but also any unsolicited comments written by the patient.

If the occurrence of AEs or SAEs is confirmed, the physician must record the events as per instructions given in [Section 7](#) of the protocol. Investigators shall not encourage the patients to change the responses reported in the questionnaire.

#### **6.6.5 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.

Data for a health economic analysis will be collected from eCRFs, most notably Hospital Discharge, Re-hospitalization and Death. Data on medical resource use will be collected for all enrolled patients from the index hospitalization at discharge and at Day 5, and then at Day 14 and through phone contact at Day 30.

The endpoints and methods of the health economic analysis will be detailed separately in the statistical analysis plan.

#### **6.6.6 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.

### **7 Safety monitoring**

All AEs 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 SAEs will be collected and databased.

Specific handling of the Study Endpoint WHF:

WHF events should be recorded not only as an endpoint but systematically as an AE as well. All WHF endpoints should thus be reported as AEs/SAEs in the AE eCRF page.



Non-serious WHF event should be reported through Day 5 and serious (SAE) WHFs should be reported through Day 14. After Day 14, only those study endpoints that qualify for SAEs and are also suspected to be related to the study medication should be reported in the AE eCRF page. It is recommended but not mandatory that the same verbatim should be used for an individual event for both the endpoint reporting and the AE reporting, i.e. “Worsening of Heart Failure”.

## 7.1 Adverse events

An AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of AEs shall be sought by non-directive questioning of the patient at each visit during the study. Adverse events may also be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of the individual patient and identifying AEs. Alert ranges for lab test abnormalities are included in [Appendix 1](#).

AEs shall be recorded in the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them accompanied by the following information.

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently significant to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the investigational treatment (no/yes)
- its duration (start and end dates). If the event is ongoing, an outcome of not recovered/not resolved shall be reported.
- whether it constitutes a SAE
- action taken regarding investigational treatment



- whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; unknown)

An SAE is any AE (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical condition(s) which meets any one of the following criteria

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

All malignant neoplasms will be assessed as serious under “medically significant” if other seriousness criteria are not met.

**Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.**

All AEs shall be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); investigational treatment dosage adjusted/temporarily interrupted; study drug(s) permanently discontinued; concomitant medication given; non-drug therapy given. The action taken to treat the AE shall be recorded on the Adverse Event eCRF.

Once an AE is detected, it shall be followed until its resolution or until it is judged to be permanent an assessment shall be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational treatment, the interventions required to treat it and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated through IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and shall be discussed with the patient during the study as needed.



The investigator shall also instruct each patient to report any new AE (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information shall be recorded in the investigator's source documents. If the AE meets the criteria of a SAE, it must however be reported to Novartis.

## **7.2 Serious adverse event reporting**

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent through Day 14 must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 14 days period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one shall be reported separately as a new event.

Information about all SAEs (either initial or follow up information) is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax numbers of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information shall be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

Follow-up information shall describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event shall be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment, a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries, except for SUSARs that are also efficacy endpoints and exempted from such expedited reporting as detailed below.





## **Study-specific expediting rules for SUSARs that are also efficacy endpoints**

In studies such as this one, where the efficacy endpoints potentially meet the requirements for SUSAR reporting, the integrity of the study may be compromised if the endpoints are systematically expedited to competent authorities/relevant ECs and investigators. In such cases, regulations allow an exemption from SUSAR expediting aimed at ensuring the validity of an outcome study (European Commission: Communication from the Commission CT-3 (2011/C 172/01); FDA Guidance 2012). Therefore, the rules for expediting SUSARs during the 14-day SAE collection period will be applied as follows.

### **1. Endpoint events that will not be expedited**

A SUSAR will not be expedited, if the event is considered consistent with one of the efficacy endpoints:

- From randomization through Day 5: renal deterioration (defined as  $\geq 0.3$  mg/dL increase in serum creatinine)
- From randomization through Day 14: in-hospital worsening heart failure (WHF) requiring rescue therapy (see endpoint definition in Section 2), or all cause death, or readmission for heart failure (HF)
- Definitions:
  - In-hospital WHF includes worsening signs and/or symptoms of heart failure that require an intensification of intravenous therapy for heart failure or assisted (invasive or non-invasive) 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.
  - HF signs and symptoms include, but are not limited to, dyspnea on exertion or at rest, orthopnea, rales, jugular venous pulse (JVP) and peripheral edema.

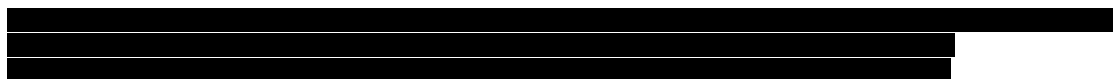
In addition, Novartis will not expedite a report to competent authorities/relevant ECs and will not issue an IN.

If specifically requested by a local Health Authority, pre-specified endpoints (see above) that also meet the criteria for SUSARs will be expedited to this Health Authority. Investigator Notifications will not be issued for these events.

### **2. Endpoint events that will be expedited**

There is a subset of SAEs, which will require expedited reporting to competent authorities/relevant ECs and investigators, if these meet SUSAR and/or endpoint criteria and are indicative of one of the following events:

- Fatal events, which are often associated with drug toxicity and which include SAEs indicative of anaphylaxis, angioedema, blood dyscrasias (including agranulocytosis, aplastic anemia, bone marrow failure, pancytopenia and bicytopenia), hepatic injury, inflammatory lung disorders (including allergic, fibrosing, necrotizing alveolitis, eosinophilic pneumonia and interstitial lung disease), rhabdomyolysis, and serious cutaneous skin reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme) torsade de pointes and prolonged QT interval.



- Efficacy endpoints, for which the investigator considers that the character and the severity of the endpoint is not consistent with the expected presentation or course of that endpoint and the investigator considers that the study drug and/or study procedures may have contributed to this abnormal presentation.

### **Study-specific expediting rules for SUSARs that are commonly observed in the study population**

In clinical trials evaluating treatments for high morbidity and/or high mortality disease states, SAEs that are known consequences of the underlying disease or condition under investigation, or events common in the study population, are anticipated to occur with some frequency during the course of the trial, regardless of drug exposure. While the investigator must still report all non-serious AEs and SAEs through Day 5, and through Day 14, respectively, SUSARS considered consistent with the following SAE Preferred Terms (PTs) will not be reported in an expedited timeframe to regulatory agencies, ECs or investigators during the course of the study:

abdominal pain, acute coronary syndrome, acute pulmonary edema, anaemia, angina pectoris \*, anxiety, arthralgia, asthenia, azotaemia, back pain, blood creatinine \*, blood pressure \*, blood urea nitrogen \*, bronchitis \*, cardiac arrest, cardiac arrhythmias (all PTs presenting any type of arrhythmia *excluding* electrocardiogram QT interval abnormal, electrocardiogram QT prolonged, long QT syndrome, torsade de pointes), cardiac asthma, cardiac failure \*, cardiac output \*, cardiac pacemaker \*, cardiac tamponade, cardiogenic shock, cardiorenal syndrome, cerebrovascular accident, chest pain, chronic obstructive pulmonary disease, confusional state, constipation, cor pulmonale \*, cough \*, creatinine renal clearance \*, delirium, diarrhea, dizziness, dyspnea \*, ejection fraction \*, fatigue, generalized oedema, glomerular filtration rate \*, gout, headache, hepatic congestion, hyperglycemia, hyperkalemia, hyperlipidemia, hypertension \*, hyperuricaemia, hypoglycemia, hypokalemia, hypernatremia, hypotension \*, implantable defibrillator \*, influenza \*, insomnia, loss of consciousness, muscle spasm, musculoskeletal pain, myocardial infarction\*, nasopharyngitis, nausea, edema, edema due to cardiac disease, edema peripheral, osteoarthritis, pain in extremity, pericardial effusion, pleural effusion, pneumonia \*, presyncope, pulmonary hypertension, pulmonary edema, renal failure \*, renal impairment, respiratory distress \*, respiratory failure \*, respiratory tract infection \*, stroke \*, syncope, transient ischemic attack, urinary tract infection, valve \*, ventricular failure \*, vomiting, weight increased.

\*More than one PT can contain this term.

If specifically requested by a local health authority, pre-specified AEs commonly observed in the study population (see above) that also meet the criteria for SUSARs will be expedited to this Health Authority. Investigator Notifications will not be issued for these events.

## **7.3 Liver safety monitoring**

### **Hepatotoxicity clinical safety standard guideline**

Hepatic dysfunction as sequelae of HF, even with modest cardiac compromise, has long been recognized. Passive hepatic congestion due to increased central venous pressure and low hepatic perfusion, reflecting impaired hemodynamics due to decreased cardiac output and profound hypotension, are considered causative mechanisms. Subsequent atrophy of liver



cells and edema of the peripheral hepatic parenchyma both lead to hepatocellular hypoxia. PaO<sub>2</sub> alterations can also add to hepatic injury. These events may be both acute with cardiac decompensation and chronic with low-grade hepatic compromise resulting in fibrosis or cirrhosis (Alvarez and Mukherjee 2011; Nikolau et al 2013).

Since cardiac-induced hepatic injury can mask hepatotoxic events, it is important to clearly determine the underlying cause of elevations of liver function tests (LFTs) that may occur during the course of this study. Therefore, to ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of hepatic events has to be followed.

The following two categories of abnormalities/liver events have to be considered during the course of the study:

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, **which cannot be solely explained by apparent cardiac decompensation as the underlying cause (i.e., another etiology is suspected to cause or contribute to this event)** and which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to [Table 14-1](#) in [Appendix 2](#) for complete definitions of liver laboratory triggers and liver events.

Every laboratory trigger or liver event **that cannot be solely explained by apparent cardiac decompensation as the underlying cause** and as defined in [Table 14-1](#) of Appendix 2 shall be followed up by the investigator or designated personnel at the trial site as summarized below. Detailed information is outlined in [Table 14-2](#) in Appendix 2.

For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation

Repeat laboratory tests should be entered on the appropriate unscheduled local laboratory CRF page.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the hepatic event that needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments and a hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded on the appropriate eCRF pages, including the liver event overview eCRF pages.



## **7.4 Pregnancy reporting**

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy shall be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment.

Any SAE experienced during pregnancy must be reported on the SAE Report Form.

## **8 Data review and database management**

### **8.1 Site monitoring**

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

### **8.2 Data collection**

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Web based software will be used: no installation procedure will be needed. Each site will be authorized by the Administrator to access into the eCRF. Each investigator site qualified personnel would be allowed to access to the eCRF by means of a



'login mask' requiring User ID and Password and it would be possible to read, modify and update only the information he/she had previously reported. All pages should report site code and patient code. On-line validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the Contract Research Organization (CRO) working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM with patient data for archiving at the investigational site.

### **8.3 Database management and quality control**

The CRO working on behalf of Novartis will review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. The Data Manager of the CRO working on behalf of Novartis will perform the cleaning session reviewing the warning messages raised by on-line checks and running post-entry checks by means of validation programs. During this process, if clarifications are needed, the Data Manager will raise queries by means of data query forms through the WEB application. Designated investigator site staff is required to respond to the query and the Data Manager will make the correction to the database on the basis of the query response. The data collection and the Queries flow as well as the on-line and off-line control checks will be detailed in the Data Management Plan and Data Validation documents

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

[REDACTED] Randomization codes and data about the study drug dispensed to the patient will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor. The IRT database will be sent electronically to Novartis (or a designated CRO). The occurrence of any protocol deviations will be reported during the conduct of the study until database lock.

After the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

### **8.4 Data Monitoring Committee**

An external independent Data Monitoring Committee (DMC) will be appointed to monitor the safety of study participants and to ensure that the program is being conducted with highest scientific and ethical standards. This DMC will review the safety data throughout the trial. Should the DMC make recommendations on the conduct of the trial that 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.

## **8.5 Adjudication Committee**

To strengthen the efficacy findings and interpretation, a Central Event Committee will be instituted and will oversee the adjudication of in-hospital WHF events and the cause of death.

A charter of responsibilities and a specific dataset to evaluate clinical cases will be available before study initiation (Endpoint Manual).

The adjudication committee will review and adjudicate all in-hospital WHF that occur through Day 5 for endpoint determination in a blind way, as well as the causes of death events. The detailed definitions of the endpoints, required documentation, and the adjudication process will be provided to all sites in a separate Endpoint Manual.

## **9 Data analysis**

All the data collected in this study will be listed and summarized as appropriate as described below. The data from all countries and all centers 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.

Subjects will be included in each efficacy analysis based on available assessments, after the data handling conventions have been applied. The prevalence approach, if not differently indicated, will be applied.

Unless stated otherwise, two-sided p values  $<0.05$  will be considered statistically significant. All statistical tables, listings and analyses will be produced using SAS® release 9.2 or later (SAS Institute, Inc, Cary, NC, USA).

More details about data analysis will be provided in the Statistical Analysis Plan.

### **9.1 Analysis sets**

The following analysis populations will be defined for statistical analysis.

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

#### **9.1.1 Full analysis set (FAS)**

The Full Analysis Set (FAS) will include randomized patients who were not mis-randomized.

Following the intent-to-treat (ITT) principle, patients are 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. The primary analysis and the analyses of all secondary and exploratory efficacy variables will be based on the FAS.



### **9.1.2 Randomized (RAN) set**

All patients who received a randomization number, regardless of receiving trial medication and including mis-randomized patients.

### **9.1.3 Per Protocol (PP) set**

The Per Protocol (PP) set will include all patients in the FAS without major protocol deviations, as will be defined in the Patient Validation Document. Results of the primary efficacy endpoints conducted in the PP set will be considered as supportive.

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

### **9.1.4 Safety population**

The safety population will include 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. The analyses on safety parameters will be conducted in the Safety set.

## **9.2 Patient demographics and other baseline characteristics**

All data about patient demographics and baseline characteristics, including derived variables, will be summarized in the FAS, overall and by treatment group, by means of summary descriptive statistics. 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.

In order to interpret the results adequately, the homogeneity of patients' distribution between treatment groups will be tested on demographics and anamnestic variables. 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, the homogeneity of data will be tested by means of t-test. If data do not respect normality assumption a Wilcoxon rank sum test will be applied. For categorical variables chi-square test will be used. Fisher exact test in case of cell frequencies less than 5 will be applied.

Whenever necessary, normality will be assessed by means of Shapiro-Wilk test and with graphical methods. In case of non-normality, appropriate transformation of data will be applied or a non-parametric test/model will be adopted.

The number and percentages of subjects meeting all eligibility criteria at screening will be provided. The number of the analysis populations will be described and the reasons excluding the patient from any particular population will be provided with the number of protocol violators per each criterion.



A complete description of patient disposition will be provided, overall and by treatment group specifying the number of randomized patients, number of patients at each visit, completed and discontinued patients, and the reason for the discontinuation.

The difference between treatment groups with respect to protocol violations and reasons for drop-out will be examined.

Medical history data will be presented by System Organ Class and Preferred Term, overall and by treatment group.

## **9.3 Treatments**

### **9.3.1 Investigational Treatment**

Overall study treatment administration details will be summarized for the FAS and the Safety population in the serelaxin arm only. This will include time from presentation to randomization (in hours), time from randomization to study treatment initiation (in hours), time from presentation to study treatment initiation (in hours), study treatment administered (yes/no), reason study treatment not administered, actual treatment received, and the number of days study treatment infused (one or two). The duration of study treatment administration (in hours) and the total volume of study treatment administered (estimated from the total time and rate of infusion) will be summarized. In addition, the number of subjects whose study medication dose was lowered or discontinued prematurely, and the reasons for discontinuation, will be summarized. Logistic regression models will be fitted considering demographics and anamnestic factors in order to identify main predictors for drug discontinuation. Odds ratio and 95% confidence intervals will be provided.

### **9.3.2 Concomitant treatments**

Concomitant treatment administration details will be collected at any time between start of screening and randomization as well as by day from randomization. It will be summarized for the FAS and the Safety population. In addition, concomitant treatment administration details collected overall during index hospitalization and after discharge will also be summarized for the FAS and the Safety population.

As a patient may have taken more than one medication, the total number of medications could be greater than the total number of subjects. Continuous variables will be summarized with standard summary statistics (number of observations, mean, standard deviation, median, first and third quartiles, minimum and maximum), categorical variables with the number and percentage of subjects taking at least one dose of medication. Percentages will be computed on patients included in the analysis population.

The total dose of IV loop diuretic and oral loop diuretic administered during the index hospitalization will be compared between treatment groups using a t-test. Doses will be converted to furosemide equivalents for analysis.

Any standard of care treatment given according to local guidelines/international standards will be summarized by preferred term.





This treatment can include but is not limited to intravenous and/or oral diuretics, ACE inhibitors/angiotensin receptor antagonists,  $\beta$  blockers, and aldosterone receptor antagonists, etc. Summary tables will also be provided by country.

As to the rescue medication usage summary statistics will be provided by treatment group. The rescue medication 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.

The use of other non-cardiovascular concomitant medications and significant non-drug therapies, prior to and after the randomization date, respectively, will be summarized by treatment group, therapeutic class, and preferred term for the FAS and the Safety population.

## **9.4 Analysis of the primary variable(s)**

The primary analysis and the analyses of all secondary and exploratory efficacy variables will be based on the FAS.

### **9.4.1 Variable(s)**

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.

A central event adjudication committee will be appointed and will oversee the WHF primary endpoint adjudication.

### **9.4.2 Statistical model, hypothesis and method of analysis**

Time to in-hospital WHF/all-cause death through Day 5 post randomization will be analyzed 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. The onset of in-hospital worsening heart failure through Day 5 will be the first assessment point, in terms of date and time, at which the investigator reported worsening heart failure (either during the initial hospitalization or re-hospitalization for heart failure). Subjects without an event will be censored at the earlier of the last assessment or 120 hours after randomization.

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  $\lambda_1$  and  $\lambda_2$  are the hazard rates for in-hospital WHF or all cause death in the standard of care group and serelaxin group, respectively. The ratio  $\lambda_2/\lambda_1$  is also called 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). Patients without an event will be censored at the earlier of the last contact date or 120 hours after randomization.

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. Absolute frequencies and proportions of patients with in-hospital WHF or all-cause death through Day 5 in each treatment group will be also provided.

### **9.4.3 Handling of missing values/censoring/discontinuations**

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

The proportions of patients with in-hospital WHF/all-cause death through Day 5 in each treatment group will be presented on all patients included in the efficacy analysis set.

### **9.4.4 Supportive analyses**

In addition to the primary analysis, the primary efficacy variable will also be analyzed using the same primary analysis model on the PP set as supportive information. Subgroup (age [65 and 75 cut off], gender, race, region, naïve vs. prior history of HF) analyses will be performed for the primary endpoint.

## **9.5 Analysis of secondary variables**

The additional efficacy endpoints will be analyzed in the FAS. Standard descriptive statistics will be presented for each treatment group at each time point the endpoint was measured.

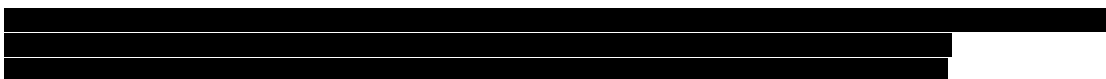
Two-sided p-values  $<0.05$  will be considered statistically significant; no adjustment for multiple comparisons will be adopted.

### **9.5.1 Efficacy variables**

#### **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 the randomization to the earlier of the onset of in-hospital WHF or death or readmission. The onset of in-hospital WHF through Day 14 will be the first assessment point,



in terms of date and time, at which the investigator reported worsening heart failure (either during the initial hospitalization or re-hospitalization for heart failure). Subjects without an event will be censored at the earlier of the last assessment or 336 hours after randomization.

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.

Absolute frequencies and proportions of patients with in-hospital WHF/all-cause death/readmission through Day 14 in each treatment group will be also provided.

### **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 vs. baseline through Day 5 (persisting need of IV therapy for HF) and at discharge in each treatment group will be provided, 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 Exact test will be used. A time-to-event analysis will be applied to provide treatment comparisons. Hazard ratios of being a responder for each of the signs and symptoms variables will be estimated using a Cox regression model with treatment as factor.

### **Renal deterioration**

Renal deterioration will be assessed as the proportion of patients with an increase of  $\geq 0.3$  mg/dL from screening in serum creatinine levels. Absolute frequencies and proportions of patients with renal deterioration at each day until Day 5, at discharge and at Day 14 in each treatment group will be provided, together with standard errors, asymptotic (Wald) and exact (Clopper-Pearson) confidence limits. The rate of renal deterioration 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 Exact test will be used.

### **Index length of hospital stay**

Index length of hospital stay (in hours) will be defined as the index discharge date and time minus the index hospitalization start date and time.

Subjects still in the hospital at Day 30 will be censored at the end of 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 (e.g. ICU, CCU, cardiology department).

### **Death through Day 30**

The time (in days) from randomization to the event will be used for analysis. Subjects without an event will be censored at the earlier of the last contact date or Day 30. 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.



## **Re-hospitalization post-discharge**

The number of re-hospitalizations per patients by treatment group will be described. Treatment groups will be compared using a Wilcoxon rank-sum test. The number of patients with 1, 2,  $\geq 2$  re-hospitalization will be summarized and treatment groups will be compared with a Chi-Square test. In case of cell frequencies less than 5, Fisher Exact test will be used.

Time to first re-hospitalization (in days) will be defined as the re-hospitalization date minus the randomization date. Subjects still in hospital at Day 30 will be censored at Day 30. Subjects who die when not hospitalized will be assigned as the date of death as their time to re-hospitalization. Treatment groups will be compared using a generalized Wilcoxon test. The Kaplan-Meier estimates for each treatment group will be plotted. Descriptive statistics by treatment group will be presented.

### **9.5.2 Safety variables**

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

#### **Physical examination**

As reported in [Section 6.5.1](#), significant findings that are present prior to signing informed consent will be included in the Medical History part of the eCRF: they will be summarized by treatment group by means of usual descriptive statistics for categorical variables. Significant findings after signing the informed consent, up to and including Day 5, which meet the definition of an AE or of a SAE, will be recorded on the Adverse Event section of the eCRF.

#### **Adverse events**

The incidence of Adverse Events (AEs) and Serious Adverse Events (SAEs) recorded during all the study will be presented.

For patients in SOC group, time of randomization will considered as time of treatment initiation. Incident AEs will be considered those AEs with an onset date and time after treatment initiation. Adverse events with an onset between informed consent and treatment initiation will be listed separately. AEs will be summarized by System Organ Class and Preferred Term. Additionally, a summary of AEs by preferred term and severity using the worst reported severity grade for each event for the subject will be provided. For analysis purposes, all AEs defined as “definite”, “probable” or “possible” will be considered as related. If the relationship to study drug is unknown or missing, the AE will be considered to be drug-related. All study-drug-related AEs, AEs with an outcome of death, AEs leading to discontinuation of treatment will be summarized by percentages and frequencies. SAEs will be summarized similarly. Percentages will be based on the number of subjects in the Safety population.

Adverse Events will be further characterized and presented according to the definitions of monitored safety risks and events of interest.

#### **Laboratory data**

Summary statistics of raw data and change from screening at each assessment time point and for each laboratory parameter will be presented by treatment group. Treatment groups will be compared for changes from screening using t-tests.



Laboratory data will also be summarized by presenting shift tables for each laboratory parameter showing the number and percentage of subjects in each treatment group with the most extreme post-screening value that falls outside extended normal ranges by the classification of subjects at screening.

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.

### **Vital signs**

Summary statistics of raw data and change from the start of screening for all patients, and from the end of screening for patients where the data are available will be provided by treatment group at each common assessment time point for vital signs, using t-tests.

### **Signs and symptoms of HF**

Summary statistics for data about signs and symptoms of HF will be provided at each assessment time point by treatment group.

### **Blood pressure decrease events**

Blood pressure values collected at various time-points only in serelaxin group during study drug infusion will be summarized by means of descriptive statistics for continuous variables.

The number and proportion of subjects who experience a confirmed blood pressure decrease event (i.e. CBPDE) during study drug infusion in the serelaxin group will be provided. Among subjects who experience a confirmed blood pressure decrease event, the events will be further characterized. Summaries will be provided separately for those confirmed events both symptomatic and asymptomatic that resulted in study drug dose reduction, and those that resulted in study drug discontinuation. The possible interaction between the effect of serelaxin and the effect of IV nitrate administration within the first 48 hours will be examined.

### **Pregnancy test results**

Any pregnancies reported will be listed and outcome reported.

## **9.5.3 Resource utilization**

Summary statistics on data about healthcare resource utilization collected through the index hospitalization, at discharge and at Day 5, and then at Day 14 and through phone contact at Day 30 will be provided by treatment group. Summary statistics for length of stay (overall and for specific inpatients care units) as well as for procedures rendered throughout the index hospitalization will be provided by treatment group. Additional information will be provided in the Statistical Analysis Plan.

## **9.5.4 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. For these scores summary statistics will be provided at each assessment by treatment group.

To compare treatment groups in quality of life change from baseline, a mixed model for repeated measures will be fitted to overall health score absolute changes (score at time of



assessment - score at screening), at Day 2, at Day 5, at discharge and Day 14 and considering value at baseline as covariate. Additional analyses will also be conducted to generate utilities per treatment group, separately for patients hospitalized and not hospitalized at study visit.

**9.5.5 Pharmacokinetics**

Not applicable.

**9.5.6 Pharmacogenetics/pharmacogenomics**

Not applicable.

[REDACTED]

**9.5.8 PK/PD**

Not applicable.

[REDACTED]

[REDACTED]

**9.6 Interim analyses**

No formal interim analyses are planned.

**9.7 Sample size calculation**

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



## **10 Ethical considerations**

### **10.1 Regulatory and ethical compliance**

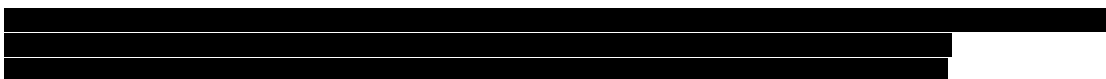
This clinical study was designed and shall be implemented and reported in accordance with the International Conference for Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21 and Japanese Ministry of Health, Labor and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

### **10.2 Informed consent procedures**

Eligible patients may only be included in the study after providing written (witnessed [by a study team independent physician or nurse for Germany only], where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient shall be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she shall indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent shall be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of childbearing potential shall be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.



## **Responsibilities of the investigator and IRB/IEC**

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

### **10.3 Publication of study protocol and results**

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

## **11 Protocol adherence**

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances shall the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as requests to approve deviations will not be granted.

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Under no circumstances shall an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the clinical study report (CSR).

### **11.1 Protocol Amendments**

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis shall be notified of this action and the IRB/IEC at the study site shall be informed within 10 working days or less, if required by local regulations.





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### 13 Appendix 1: Clinically notable laboratory values

Clinically notable laboratory abnormalities for selected tests based on a percent change from baseline:

#### Hematology

RBC count	>50% increase, >25% decrease
Hemoglobin	>50% increase, >25% decrease
Hematocrit	>50% increase, >25% decrease
WBC count	>100% increase, >50% decrease
Platelet count	>100% increase, >50% decrease

#### Blood Chemistry

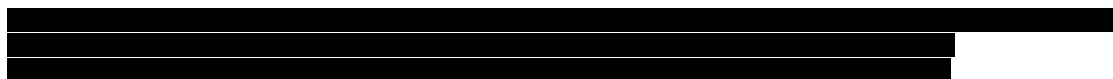
ALT (SGPT)	See <a href="#">Section 7.3</a> Liver safety monitoring and <a href="#">Tables 14-1, 14-2</a> in Appendix 2
AST (SGOT)	See <a href="#">Section 7.3</a> Liver safety monitoring and <a href="#">Tables 14-1, 14-2</a> in Appendix 2
BUN	>100% increase
Creatinine	>100% increase
Total bilirubin	See <a href="#">Section 7.3</a> Liver safety monitoring and <a href="#">Tables 14-1, 14-2</a> in Appendix 2
Alkaline phosphatase	>100% increase
Potassium	>25% increase, >25% decrease
Calcium	>20% increase, >20% decrease
Uric acid	>100% increase



## 14 Appendix 2: Liver laboratory trigger and liver event definitions and follow-up requirements

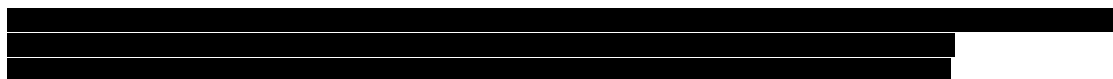
**Table 14-1** Definitions of liver laboratory triggers or liver events, which cannot be solely explained by apparent cardiac decompensation as the underlying cause (i.e., another etiology is suspected to cause or contribute to this event)

	Definition/ threshold
LIVER LABORATORY TRIGGERS	<ul style="list-style-type: none"><li>• <math>3 \times \text{ULN} &lt; \text{ALT} / \text{AST} \leq 5 \times \text{ULN}</math></li><li>• <math>1.5 \times \text{ULN} &lt; \text{TBL} \leq 2 \times \text{ULN}</math></li></ul>
LIVER EVENTS	<ul style="list-style-type: none"><li>• <math>\text{ALT}</math> or <math>\text{AST} &gt; 5 \times \text{ULN}</math></li><li>• <math>\text{ALP} &gt; 2 \times \text{ULN}</math> (in the absence of known bone pathology)</li><li>• <math>\text{TBL} &gt; 2 \times \text{ULN}</math> (in the absence of known Gilbert syndrome)</li><li>• Potential Hy's Law cases (defined as <math>\text{ALT}</math> or <math>\text{AST} &gt; 3 \times \text{ULN}</math> and <math>\text{TBL} &gt; 2 \times \text{ULN}</math> [mainly conjugated fraction] without notable increase in <math>\text{ALP}</math> to <math>&gt; 2 \times \text{ULN}</math>)</li><li>• Any clinical event of jaundice (or equivalent term)</li><li>• <math>\text{ALT}</math> or <math>\text{AST} &gt; 3 \times \text{ULN}</math> accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia</li><li>• Any adverse event potentially indicative of a liver toxicity *</li></ul>



**Table 14-2 Follow up requirements for liver laboratory triggers or liver events, which cannot be solely explained by apparent cardiac decompensation as the underlying cause (i.e., another etiology is suspected to cause or contribute to this event)**

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case <sup>a</sup>	<ul style="list-style-type: none"> <li>Discontinue the study drug immediately</li> <li>Hospitalize, if clinically appropriate</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	ALT, AST, fractionated bilirubin <sup>d</sup> , Alb, PT/INR, ALP and $\gamma$ GT until resolution <sup>c</sup> (frequency at investigator discretion)
<b>ALT or AST</b>		
> 8 × ULN	<ul style="list-style-type: none"> <li>Discontinue the study drug immediately</li> <li>Hospitalize if clinically appropriate</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	ALT, AST, fractionated bilirubin <sup>d</sup> , Alb, PT/INR, ALP and $\gamma$ GT until resolution <sup>c</sup> (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	<ul style="list-style-type: none"> <li>Repeat LFT within 48 hours</li> <li>If elevation persists, continue follow-up monitoring</li> <li>If elevation persists for <i>more than 2 weeks</i>, discontinue the study drug</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	ALT, AST, fractionated bilirubin <sup>d</sup> , Alb, PT/INR, ALP and $\gamma$ GT until resolution <sup>c</sup> (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms <sup>b</sup>	<ul style="list-style-type: none"> <li>Discontinue the study drug immediately</li> <li>Hospitalize if clinically appropriate</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	ALT, AST, fractionated bilirubin <sup>d</sup> , Alb, PT/INR, ALP and $\gamma$ GT until resolution <sup>c</sup> (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	<ul style="list-style-type: none"> <li>Repeat LFT within the next week</li> <li>If elevation is confirmed, initiate close observation of the patient</li> </ul>	Investigator discretion Monitor LFT within 1 to 4 weeks
<b>ALP (isolated)</b>		
> 2 × ULN (in the absence of known bone pathology)	<ul style="list-style-type: none"> <li>Repeat LFT within 48 hours</li> <li>If elevation persists, establish causality</li> <li>Complete liver CRF</li> </ul>	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
<b>TBL (isolated)</b>		
> 2 × ULN (in the absence of known Gilbert syndrome)	<ul style="list-style-type: none"> <li>Repeat LFT within 48 hours</li> <li>If elevation persists, discontinue the study drug immediately</li> <li>Hospitalize if clinically appropriate</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	ALT, AST, fractionated bilirubin <sup>d</sup> , Alb, PT/INR, ALP and $\gamma$ GT until resolution <sup>c</sup> (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN	<ul style="list-style-type: none"> <li>Repeat LFT within the next week</li> <li>If elevation is confirmed, initiate</li> </ul>	Investigator discretion Monitor LFT within 1 to 4 weeks





Criteria	Actions required	Follow-up monitoring
(patient is asymptomatic)	close observation of the patient	or at next visit
Jaundice	<ul style="list-style-type: none"> <li>Discontinue the study drug immediately</li> <li>Hospitalize the patient</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	ALT, AST, fractionated bilirubin <sup>d</sup> , Alb, PT/INR, ALP and $\gamma$ GT until resolution <sup>c</sup> (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	<ul style="list-style-type: none"> <li>Consider study drug interruption or discontinuation</li> <li>Hospitalization if clinically appropriate</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	Investigator discretion

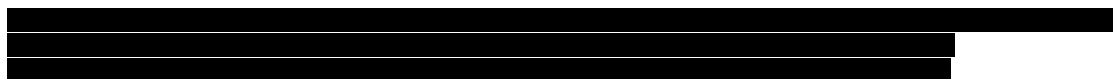
\*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

<sup>a</sup>Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

<sup>b</sup>(General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

<sup>c</sup>Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

<sup>d</sup>Fractionated bilirubin includes testing for total bilirubin, direct bilirubin, and indirect bilirubin



## 15 Appendix 3: Physician assessment of signs and symptoms

The following criteria are to be used to assess patient's signs and symptoms of heart failure.

Exertional Dyspnea: The subject should be queried as to the extent of dyspnea noted over the preceding 1-3 hours as follows:

0	No exertional dyspnea (NYHA Class I equivalent)
1	Mild exertional dyspnea, occurring with moderate exertion (climbing stairs or equivalent-NYHA Class II equivalent)
2	Moderate exertional dyspnea, occurring with only mild exertion (walking-NYHA Class III equivalent)
3	Severe exertional dyspnea, occurring at rest (NYHA Class IV)

Orthopnea: The subject should be observed after being in the lowest recumbent position for 10-15 minutes or queried in order to determine the minimum number of "pillows" required to obtain/maintain comfort while supine. This should be graded on a 0 - 4 scale as follows:

0	Comfortable with no pillow or very minimal elevation of head
1	Comfortable with no less than one pillow to elevate head (approx 10 cm elevation)
2	Comfortable with no less than two pillows to elevate head (approx 20 cm elevation)
3	Comfortable with head no less than at 30 degree elevation

Rales: Auscultation of the lungs applying a 4-point scale:

0	No rales heard, either moist or dry, after clearing with cough anywhere in the lung fields
<1/3	Moist or dry rales heard in the lower 1/3 of either or both lung fields that persist after a cough in attempt to clear
1/3-2/3	Moist or dry rales heard throughout the lower half to 2/3 of either or both lung fields
>2/3	Moist or dry rales heard throughout both lung fields



Jugular venous pulse (JVP): With the subject supine at approximately a 45-degree angle, examination of the JVP is performed and the estimation, in cm H<sub>2</sub>O, is converted into one of 3 categories:

<6 cm H <sub>2</sub> O	Complete absence of discernable venous wave throughout respiratory cycle above the clavicle, even with hepatic compression (HJR)
6-10 cm H <sub>2</sub> O	Venous wave detectable above the clavicle, at least during expiration and possibly throughout respiratory cycle but less than 4 cm above the clavicle (<10 cm H <sub>2</sub> O). Presence of venous wave only with mild HJR should be graded in this category.
>10 cm H <sub>2</sub> O	Presence of venous wave throughout respiratory cycle with wave sometimes $\geq$ 4 cm H <sub>2</sub> O above clavicle and typically increased with HJR. Patients with values of 6-10 cm H <sub>2</sub> O and positive HJR should be graded in this category.
NA	Examination could not be performed/result unobtainable

Peripheral Edema, Pre-sacral Edema: Edema should be examined in any dependent area including the lower extremities or the sacral region. The range to be applied is 0 - 3 (4 point scale).

0	The complete absence of edema, as determined by applying mild digital pressure in all dependent areas and failing to elicit any indentation of skin and subcutaneous tissues.
1+	Detection of limited areas where mild digital pressure elicits an indentation of skin and subcutaneous tissues that resolves over approximately 10-15 seconds. Edema of this grade is typically limited to only the lower extremities or only the sacrum, not both.
2+	Detection of moderate surface area in one or both areas (sacrum and lower extremities) where indentations of skin and subcutaneous tissues are easily created with limited pressure and these indentations disappear slowly (15-30 seconds or more).
3+	Large areas of lower extremities (and sacrum if subject has been recumbent), often to mid-calf or higher, having easily produced and slowly resolving (more than 30 seconds) indentations. This extent of edema is sometimes associated with acute or subacute skin changes including weeping of skin and/or skin break down.

Patient's assessment of dyspnea: Patient should be asked to assess their level of shortness of breath compared to admission using a scale from 0 to 10 where 0=none to 10=very very severe (maximal).



