NOVARTIS

Clinical Development

RLX030A

Clinical Trial Protocol CRLX030A2301 / NCT01870778

A multicenter, randomized, double-blind, placebo-controlled phase IIIb study to evaluate the efficacy, safety and tolerability of Serelaxin when added to standard therapy in acute heart failure patients

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List of abbreviations

AE	Adverse event
AHF	Acute heart failure
Alb	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
b.i.d.	twice a day
CCU	Coronary care unit
CRF	Case Report/Record Form (paper or electronic)
CPO	Country Pharma Organization
CRO	Contract Research Organization
CV	Cardiovascular
DS&E	Drug Safety & Epidemiology
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ER	Emergency Room
ED	Emergency Department
HF	Heart failure
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
i.v.	intravenous
IRB	Institutional Review Board
IRT	Interactive Randomization Technology
ICU	Intensive Care Unit
LFT	Liver function test
LOS	Length of stay
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume

MedDRA	Medical dictionary for regulatory activities
o.d.	once a day
p.o.	oral
PT	Preferred Term
RF	Renal failure
SAE	Serious adverse event
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
ULN	Upper limit of normal
WHF	Worsening heart failure
γGT	Gamma-glutamyltransferase

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	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)
Epoch	The planned stage of the patients' 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 on patients after treatment has ended.
Investigational drug	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."
Investigational treatment	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 *does not include* other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Subject Number	A number assigned to each patient who enrolls into the study
Part	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.
Period	A subdivision of a cross-over study
Premature patient withdrawal	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)
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study/investigational treatment was discontinued whichever is later
Study drug/ treatment	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
Study/investigational treatment discontinuation	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
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

Protocol synopsis

Protocol number	CRLX030A2301
Title	A multicenter, randomized, double-blind, placebo-controlled phase IIIb study to evaluate the efficacy, safety and tolerability of Serelaxin when added to standard therapy in acute heart failure patients
Brief title	Efficacy, safety and tolerability of Serelaxin when added to standard therapy in acute heart failure
Sponsor and Clinical Phase	Novartis/3b
Investigation type	Biologic/Vaccine
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the efficacy, safety and tolerability of intravenous infusion of 30 µg/kg/day serelaxin administered by body weight category (Table 5-3) for 48 hours, when added to standard therapy, in approximately 6,800 acute heart failure (AHF) patients. Efficacy will be determined based on the relative reduction in CV death, worsening heart failure and other clinical outcomes through a follow-up period of 180 days, as compared to placebo. The rate of mortality in AHF remains high despite contemporary standard-of-care management, which has not changed significantly in the last 10 years, and represents a key unmet need for AHF patients. In the RELAX AHF trial a clinically and statistically significant 37% reduction in both CV and all-cause mortality through Day 180 were seen. Data from this study is intended to replicate the reduction in mortality in AHF patients observed in the RELAX AHF trial. The reduction in worsening heart failure through Day 5 is a potential efficacy benefit which is evolving among the scientific community as an increasingly clinically relevant treatment goal of AHF. Following initial stabilization, in-hospital WHF occurs in 10- 30% of hospitalized patients reflecting a severe manifestation of the AHF disease continuum requiring immediate intensification of rescue therapy (Torre-Amione et al 2009, Cotter et al 2010, Metra et al 2010a, Teerlink et al 2013) and represents another key unmet need for AHF patients.
Primary Objective(s) and Key Secondary Objective	**Primary Objectives** • To demonstrate that serelaxin is superior to placebo in reducing CV death in AHF patients during a follow-up period of 180 days • To demonstrate that serelaxin is superior to placebo in reducing WHF through Day 5. **Key secondary objectives** • To demonstrate that serelaxin is superior to placebo in reducing all-cause mortality during a follow-up period of 180 days • To demonstrate that serelaxin is superior to placebo in reducing the length of total hospital stay during the index AHF hospitalization • To demonstrate that serelaxin is superior to placebo in reducing the composite endpoint of CV death or rehospitalization due to heart failure/renal failure, during a follow-up period of 180 days
Secondary Objectives	**Efficacy**

	• To demonstrate that serelaxin is superior to placebo in reducing the length of ICU and/or CCU stay during the index AHF hospitalization • To demonstrate that serelaxin is superior to placebo in relieving signs and symptoms of congestion through Day 5 • To compare serelaxin to placebo in the changes of selected biomarkers in a subset of randomized patients **Safety** • To evaluate the safety and tolerability of intravenous serelaxin in AHF patients
Study design	This is a multicenter, randomized, double-blind, placebo-controlled study
Population	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.
Inclusion criteria	1. Male or female ≥18 years of age who sign the informed consent, with body weight ≤160 kg 2. Hospitalized for AHF with the anticipated requirement of intravenous therapy (including IV diuretics) for at least 48 hours; AHF is defined as including all of the following measured at any time between presentation (including the emergency department) and the end of screening: • Persistent dyspnea at rest or with minimal exertion at screening and at the time of randomization, despite standard background therapy for acute heart failure including the protocol required intravenous furosemide of at least 40 mg total (or equivalent). • Pulmonary congestion on chest radiograph • BNP ≥ 500 pg/mL or NT-proBNP ≥2,000 pg/mL; for patients ≥ 75 years of age or with current atrial fibrillation (at the time of randomization), BNP ≥ 750 pg/mL or NT-proBNP ≥ 3,000 pg/mL*** 3. Systolic BP ≥125 mmHg at the start and at the end of screening and impaired renal function defined as an eGFR*** between presentation and randomization of ≥ 25 and ≤75mL/min/1.73m^2, calculated using the sMDRD equation 4. Able to be randomized **within 16 hours** from presentation to the hospital, including the emergency department** 5. Received intravenous furosemide of at least 40 mg total (or equivalent) at any time between presentation (this includes outpatient clinic, ambulance, or hospital including emergency department) and the start of screening for the study for the treatment of the current acute HF episode. Time from presentation to start of furosemide administration must be less than 6 hours. *** 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 prior to arrival at the hospital (this includes outpatient clinic, ambulance, or hospital including emergency department) for the current acute HF episode.* ****Assessed based on local laboratory*

Exclusion criteria	1. Dyspnea due to non-cardiac causes such as acute or chronic respiratory disorders or infections (i.e., severe chronic obstructive pulmonary disease, bronchitis, pneumonia), 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 or oral steroids (does not include inhaled steroids); need for intubation or the current use of IV or oral steroids for COPD 3. Patients with blood pressure > 180 mmHg at the time of randomization 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. Clinical evidence of acute coronary syndrome currently or within 30 days prior to enrollment. (Note: 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.) 6. 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 7. Patients with severe renal impairment defined as pre-randomization eGFR < 25 mL/min/1.73m^2 calculated using the sMDRD equation, and/or those receiving current or planned dialysis or ultrafiltration 8. Patients with hematocrit <25%, or a history of blood transfusion within the 14 days prior to screening, or active life-threatening GI bleeding. 9. Known hepatic impairment (as evidenced by total bilirubin > 3 mg/dL, or increased ammonia levels, if performed) or history of cirrhosis with evidence of portal hypertension such as varices. 10. Significant, uncorrected, left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy or severe aortic stenosis (i.e., aortic valve area <1.0 cm^2 or mean gradient >40 mmHg on prior or current echocardiogram), and severe mitral stenosis 11. Severe aortic insufficiency or severe mitral regurgitation for which surgical or percutaneous intervention is indicated. 12. Documented, prior to or at the time of randomization, restrictive amyloid myocardiopathy, OR acute myocarditis or hypertrophic obstructive, restrictive, or constrictive cardiomyopathy (does NOT include restrictive mitral filling patterns seen on Doppler echocardiographic assessments of diastolic function).

	13. 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 (endotracheal intubation, mechanical ventilation; intra-aortic balloon pump or any ventricular assist device; hemofiltration, ultrafiltration or dialysis), with the exception of IV furosemide (or equivalent), or IV nitrates at a dose of ≤ 0.1 mg/kg/hour if the patient has a systolic BP >150 mmHg at the start of screening. 14. Any major solid organ transplant recipient or planned/ anticipated organ transplant within 1 year or Major surgery, including implantable devices (e.g. ICD, CRT), or major neurologic event including cerebrovascular events, within 30 days prior to screening 15. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past year with a life expectancy less than 1 year 16. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study treatment plus 5 days after cessation of study drug. 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 hCG laboratory test. . Highly effective contraception methods total abstinence, male/female sterilization and a combination of the following a+b or a+c or b+c). Refer to Section 4.2 Exclusion Criteria #18. 17. Any other medical condition(s) 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 understand and comply with the protocol instructions or follow-up procedures.
Investigational and reference therapy	• Serelaxin (30 µg/kg/day) administered by body weight category (Table 5-3) infused over 48 hours • Placebo
Efficacy assessments	Primary efficacy assessments: • Time to confirmed CV death during a follow-up period of 180 days • Time to first occurrence of worsening heart failure* through Day 5 (considering death in the 5-day period as WHF event) Key secondary efficacy assessments: • Time to all-cause death during a follow-up period of 180 days • Length of total hospital stay for the index AHF hospitalization • Time to first occurrence of the composite endpoint of CV death or rehospitalization due to heart failure/renal failure, during a follow-up period of 180 days.

	* *Worsening heart failure 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 ventilatory, renal or circulatory support. Such treatment can include the institution or up-titration of IV diuretic, IV nitrates or any other IV medication for heart failure, or institution of mechanical support such as mechanical ventilation, ultrafiltration, hemodialysis, intra-aortic balloon pump or ventricular assist device, etc. WHF can occur either during the index admission, or after discharge as an unplanned rehospitalization or unscheduled physician office/emergency department visit due to a primary diagnosis of HF. This endpoint also includes patients who die in this 5-day period of any cause before experiencing episode(s) of WHF.* Other secondary efficacy assessments: • Length of ICU and/or CCU stay for the index AHF hospitalization • Change from baseline in congestive signs and symptoms of HF through Day 5 • Change from baseline in selected biomarkers from baseline through Day 14 in a subset of randomized patients
Safety assessments	• Physical examination • Vital signs • Height and weight • Laboratory evaluations • Electrocardiogram
Other assessments	• Echocardiogram • Healthcare resource utilization (RU parameters)
Data analysis	The primary efficacy variables will be the time to confirmed CV death during the follow-up period of 180 days and time to worsening heart failure through Day 5. For CV death, time-to-event is computed as the number of days from randomization to CV death. Patients without an event will be censored at the earlier of the last date at which the vital status was known or Day 180. Patients who die from a non-cardiovascular cause before Day 180 will be censored at the time of death. The statistical hypothesis is: H_0: $\lambda_2/\lambda_1 \geq 1$, i.e., the rate of primary event of CV death is greater or equal in the serelaxin group relative to the placebo group *versus the one-sided alternative* H_A: $\lambda_2/\lambda_1 < 1$, i.e., the rate of CV death is smaller in the serelaxin group relative to the placebo group, where λ_1 and λ_2 are the hazard rates for CV death in the placebo group and serelaxin group, respectively. The ratio λ_2/λ_1 is also called the hazard ratio of serelaxin to placebo. The hypothesis will be tested based on the FAS with a logrank test at an initial significance level of (4/5)α within a sequentially rejective multiple testing procedure. (See Section 10.5.1). Note that the significance level for the final test will be adjusted to account for, the planned interim analysis. Time to worsening heart failure through Day 5 will be analyzed using Gehan's generalized Wilcoxon test at an initial significance level of (1/5)α within a sequentially rejective multiple testing procedure. (See Section 10.5.1).

	The key secondary efficacy endpoint of all-cause mortality through Day 180 will not be formally incorporated in a multiple testing procedure. It will be tested with a full α (two-sided) by itself if one of the primary endpoints is statistically significant. A sequentially rejective multiple testing procedure (Bretz, F et al 2009) is used in order to control the overall α across the primary variables and the other two key secondary variables, length of hospital stay (LOS) and composite of CV death or rehospitalization due to HF/RF (CVDR). Although there are two primary endpoints in this trial, the sample size is calculated based on CV death only. This is an event-driven trial with fixed maximum duration of 180 day follow-up period for each patient. The 180-day CV death rate is assumed to be 9.0% in the placebo group. [redacted] Using the proposed multiple testing procedure, the power for WHF is at least 80% with this sample size assuming at least 20% RRR and 12.2% placebo event rate for WHF.
Key words	Acute Heart Failure (AHF), Renal Impairment, Worsening Heart Failure,

Amendment 5

Prevention of in-hospital WHF events is increasingly being recognized as a clinically relevant treatment goal of AHF. Following initial stabilization, in-hospital WHF occurs in 10-30% of hospitalized patients reflecting a severe manifestation of the AHF disease continuum requiring immediate intensification of rescue therapy (Torre-Amione et al 2009, Cotter et al 2010, Metra et al 2010a, Teerlink et al 2013) and represents a key unmet need for AHF patients. Thus after further consideration, the Executive Committee has recommended including the reduction of WHF events through day 5 as an additional primary endpoint. The following changes were made:

Sections 2.1 and 2.2 were updated to add reduction in worsening heart failure through Day 5 as a primary objective and delete it from the key secondary objectives.

Section 3.1 was updated to change the target number of CV deaths and the sample size needed to adjust for the alpha-split required to accommodate the additional primary objective.

Section 3.2 was updated to add WHF to the primary objective and include the WHF rationale.

Section 4 was changed to update the target number of CV deaths and the sample size needed to adjust for the alpha-split required to accommodate the additional primary objective.

Section 6.4.1 and 6.4.2 were updated to add the reduction in worsening heart failure through Day 5 as a primary objective and delete it from the key secondary objectives.

Sections 10.4.1, 10.4.2, 10.4.3, 10.4.4, and 10.5.1 were updated to define the statistical analysis of the new additional primary endpoint.

Section 10.6 was revised to update the type 1 error for the interim analysis.

Section 10.7 was revised to define the alpha-split for the two primary endpoints. The sample size calculation was also revised to define the additional patients needed to accommodate the additional primary endpoint.

In addition to the changes related to elevating WHF to an additional primary endpoint, changes were made to Sections 6, 6.4.4, 6.5.1, 6.5.2, 6.5.3, 6.5.4, 6.6.6 and Table 6-1 to provide some clarity and flexibility around the conduct and timing the study visits and visit procedures.

The following additional minor changes were also made:

- Throughout the document, worsening of heart failure was changed to worsening heart failure.
- Section 1.1 minor grammatical changes were made.
- Section 4.1 was changed to clarify that the time from presentation to start of furosemide *must* be less than 6 hours.
- Section 4.2 was updated to clarify the following exclusion criteria:
  - Criteria 2: …. use of IV or oral steroids *(does not include inhaled steroids);*
  - Criteria 10: mean gradient for the aortic valve area was changed to >40mmHg
  - Criteria 13: *diuretic* was added to the description of equivalent for IV furosemide

- Criteria 16 *current* and *due to the malignancy* was added to life expectancy less than 1 year

- Section 5.3 was updated to clarify that the misrandomized patients *should have been* considered screen failures.
- Section 5.5.9 was updated to clarify patient withdrawals and continued patient follow-up.
- Additional references were added to the reference list.

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. In addition, if 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 amended protocol.

Amendment 4

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, to improve the overall clarity of the study inclusion and exclusion criteria, the study Executive Committee recommended the following changes:

Inclusion criteria:

- The criteria for hospitalization due to AHF was enhanced to read: hospitalized for AHF with the anticipated requirement of intravenous therapy (including IV diuretics) for at least 48 hours;
- The dyspnea at rest criteria was enhanced to read: persistent dyspnea at rest or with minimal exertion at screening and at the time of randomization, despite standard background therapy for acute heart failure including the protocol required intravenous furosemide of at least 40 mg total (or equivalent).
- The BNP and NT proBNP criteria were increased to BNP ≥ 500 pg/mL or NT-proBNP ≥2,000 pg/mL. The following BNP and NT proBNP criteria were also added: for patients ≥ 75 years of age or with current atrial fibrillation (at the time of randomization), BNP ≥ 750 pg/mL or NT-proBNP ≥ 3,000 pg/mL
- The inclusion criteria for intravenous furosemide was updated to add the following criteria: Time from presentation to start of furosemide administration should be less than 6 hours.

Exclusion criteria:

The following exclusion criteria were updated:

- The dyspnea primarily due to non-cardiac causes was enhanced to read: Dyspnea due to non-cardiac causes such as acute or chronic respiratory disorders or infections (i.e., severe chronic obstructive pulmonary disease, bronchitis, pneumonia), which may interfere with the ability to interpret the primary cause of dyspnea.
- "Uncorrected" was added to the significant, left ventricular outflow obstruction, criteria.
- The criteria for current or planned treatment with IV vasoactive therapies was updated to clarify that the use of IV nitrates is permitted if the patient has systolic BP > 150 mmHg at "the start of " screening.
- The criteria for other medical conditions that put the patient at risk or influence study results was updated to include drug or alcohol abuse or psychiatric, behavioral or cognitive disorders sufficient to interfere with the patient's ability to understand and comply with the protocol instructions or follow up procedures.

The following exclusion criteria were added:

- Known history of respiratory disorders requiring the daily use of IV or oral steroids; need for intubation or the current use of IV or oral steroids for COPD
- Patients with blood pressure > 180 mmHg at the time of randomization or persistent heart rate >130 bpm.

- Known hepatic impairment (as evidenced by total bilirubin > 3 mg/dL, or increased ammonia levels, if performed) or history of cirrhosis with evidence of portal hypertension such as varices.
- Severe aortic insufficiency or severe mitral regurgitation for which surgical or percutaneous intervention is indicated.
- Documented, prior to or at the time of randomization, restrictive amyloid myocardiopathy, OR acute myocarditis or hypertrophic obstructive, restrictive, or constrictive cardiomyopathy (does NOT include restrictive mitral filling patterns seen on Doppler echocardiographic assessments of diastolic function).

The following exclusion criteria were also updated and added to comply with the most recent Novartis standard guidelines for managing patients of child-bearing potential:

Updated:

- The criteria for women of child-bearing potential, was updated to require the use of highly effective methods of contraception during dosing of study treatment plus 5 days after cessation of study drug. The methods for effective contraception were also updated to define a combination of criteria required.

Added:

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

Section 5.3 was updated to clarify the management of misrandomized patients.

Section 5.5.4 was modified to remove the requirement for infusion bags containing similar polymeric materials. There is no restriction for use of any other 250 mL infusion bag with 5% dextrose.

Minor modifications were made to the assessment of AHF signs and symptoms to clarify who besides the PI can perform the assessment of signs and symptoms (Section 6.4.4), and to the vital signs section to clarify what assessments are performed at all timepoints (Section 6.5.2).

Section 7.2 was updated to define the process for managing local SUSAR reporting.

Section 7.3 Liver safety monitoring, and Section 15 Appendix 2 Liver event definitions, were amended to update the guidelines for liver safety monitoring to conform to the updated Novartis standard liver monitoring guidelines.

As per feedback from the FDA, Amendment 2 was issued to change Section 10.5 of the protocol to include all four key secondary efficacy variables in the multiple testing procedure so the overall type I error including all-cause death and other three key efficacy variables is controlled at 5% alpha level. Subsequent to the change, the FDA indicated that this change to the protocol was not required. So Section 10.5 has been amended again to return to the initial testing procedure where all-cause death through Day 180 is not included in the multiple testing

procedure of the key secondary efficacy variables, i.e, only the other three key secondary efficacy variables are included in the multiple testing procedure.

Section 10.5 was further updated to include sensitivity analyses of WHF using a modified definition of WHF, for example where both signs and symptoms are present.

Section 10.7 Table 10-2 was also update to reflect the powers of the key secondary variables on the selected scenarios.

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Amendment 3

Amendment rationale and major changes

In the original protocol, exclusion criteria #8 states:

> current (within 2 hours prior to screening) or planned (through completion of study drug infusion) treatment with any IV vasoactive therapies, including vasodilators (including nesiritide), positive inotropic agents and vasopressors, or mechanical support (endotracheal intubation, mechanical ventilation; intro-aortic balloon pump or any ventricular assist device; hemofiltration, ultrafiltration or dialysis), with the exception of IV furosemide (or equivalent), or IV nitrates at a dose of ≤ 0.1 mg/kg/hour if the patient has a systolic BP > 150 mmHg at screening.

To improve patient recruitment, the study Executive Committee has recommended to amend this exclusion criteria to exclude current treatment within 2 hours prior to randomization (and not at screening). In addition, a few minor updates have been made to the protocol in the following areas:

- Section 5.5.4 has been updated to include additional information about 5% dextrose infusion bags and materials which can be used during preparation of study treatment
- Table 5-2 filter name has been updated based on the availability of a new brand name
- Section 6.5.1, the timing of the physical exam was clarified due to inconsistency with table 6-1 (schedule of assessments).
- Amendment 2 summary of amendment was updated to remove the requirement for IRB/EC protocol approval prior to implementation since this is not valid in select countries
- Table 6-1 schedule of assessments table has been updated to clarify the intervals for collection of worsening heart failure assessment (at hours 24, 48, 72, 96 and 120) as part of the physician assessment of HF signs and symptoms
- Section 10.1 safety set definition has been updated to clarify a statement that any patient who has received serelaxin will be included as part of the serelaxin treatment group
- Section 10.5.1 time-to-event has been changed to be defined as randomization to the event
- Section 10.5.1 length of stay definition has been changed to index hospitalization discharge date and time minus the randomization date and time

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.

Amendment 2

Short summary of the amendment rationale and major changes

In the current protocol, all-cause death through Day 180 is not included in the multiple testing procedure of the key secondary efficacy variables, i.e, only the other three key secondary efficacy variables are included in the multiple testing procedure. As per feedback from FDA, Section 10.5 of the protocol has been amended to include all four key secondary efficacy variables in the multiple testing procedure, so the overall type I error including all-cause death and other three key efficacy variables is controlled at 5% alpha level.

In addition a minor change was made to the Physician assessment of signs and symptoms criteria located in Section 16, Appendix 3. NA, not evaluable, was removed from the assessments for exertional dyspnea and orthopnea. This was done to avoid confusion during data collection between when the evaluation was not evaluable (subject was immobile) and when the evaluation was simply not done.

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. In addition, if 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 amended protocol.

Summary of previous amendments

Amendment 1

Amendment rationale

In order to comply with Health Authority requests stemming from the Volunteer Harmonization Procedure (VHP), the following changes have been made throughout the protocol.

- A criteria was added excluding patients with hematocrit <25%, or a history of blood transfusion within the 14 days prior to screening, or active life-threatening GI bleeding
- The protocol was updated to include ECG assessments at screening and at Day 5 or discharge, whichever occurs first. ECGs will be performed and interpreted locally, and the interpretation and person interpreting the ECG will be recorded in the source documents.
- The protocol was updated to include an echocardiogram. The echo will be performed during the index hospitalization, to determine a patient's ejection fraction which will be used to classify the type of heart failure for subgroup analysis. The echocardiogram should be performed as soon as possible post randomization, but prior to discharge. If an echocardiogram is performed during the screening period (i.e. within the 16 hours window) and the patient is subsequently randomized, the screening echocardiogram will qualify as the index hospitalization echocardiogram and a repeat echocardiogram post randomization will not be necessary.
- The protocol was updated to change the follow up period, if following the interim analysis the trial is concluded early for efficacy, from a minimum of 14 days to 180 days.

- A minor clarification was made to the timing of the ECG substudy in the Assessment Schedule and substudy description. The first substudy ECG should be performed at baseline, not at screening.
- A minor clarification was made to the Laboratory substudy urine assessment in the Assessment Schedule to reflect that the data is to be maintained in the source documents only and not in the database (X was changed to S).

1 Introduction

1.1 Background

Acute heart failure (AHF) is a major public health problem associated with high mortality, morbidity, and financial costs. It is already the most common and most expensive cause of hospitalization and rehospitalization in patients 65 years and older (Hunt et al 2009, Jencks S NEJM). With the aging of the population, the prevalence of HF is projected to increase by 25% over the next 20 years (Heidenreich et al 2011). As such, the burden of HF for health care systems will also increase.

AHF is defined as the rapid onset of, or change in, signs and symptoms of HF requiring urgent therapy, which usually results in hospitalization (McMurray et al 2012). Recent HF registries demonstrate that more than 80% of AHF patients present with dyspnea, 60-80% with renal impairment, and >50-75% with normal to elevated systolic BP (Adams et al 2005, Gheorghiade et al 2006a, Gheorghiade et al 2006b, Gheorghiade et al 2009). Although there are multiple precipitants of AHF, ultimately AHF results in (1) pulmonary, central and/or peripheral venous congestion and (2) hypoperfusion, both of which can induce end organ damage and metabolic abnormalities. The pathophysiology of AHF is complex, including processes such as abnormal ventricular systolic and/or diastolic function, myocardial injury as manifested by elevation of circulating cardiac troponin, vascular changes such as endothelial dysfunction, increased aortic impedance and left ventricular afterload, renal dysfunction precipitating sodium and fluid retention, as well as neurohormonal and inflammatory activations (Metra et al 2010a; Metra et al 2012).

Although symptomatic improvement occurs in most patients following currently available AHF therapy within a few days of admission, such improvement is usually incomplete. Persistent or recurrent HF symptoms both during and after hospitalization likely contribute to the downward-spiral of disease progression with poor clinical outcomes. In the IMPACT-HF trial, 60% of patients were discharged with continuing symptoms of dyspnea or fatigue, and after 60 days, 45% had worsening of HF symptoms with 25% of patients rehospitalized (Gheorghiade, 2006). The presence of worsening HF symptoms confers a worse prognosis for AHF patients (Damman et al 2007; Metra et al 2008). Overall, the mortality in AHF patients remains very high, e.g. 30 day, 1 year and 5 year mortalities are reportedly 10.4%, 22% and 42.3% (Lloyd-Jones 2010). Post-discharge rehospitalization afflicts up to 1/3 of patients (Gheorghiade, 2006). Despite a decade of efforts, outcome from AHF remain dismal.

The main clinical challenges in AHF management are to achieve optimal and sustained resolution of congestion to improve symptoms, prevent in-hospital worsening heart failure and end organ dysfunction or damage, prevent rehospitalization, and most importantly, reduce both short- and intermediate-term mortality. However, current standard-of-care for AHF offers few options, if any to meet these challenges. Therapies used 4 decades ago are the same therapies used today: oxygen, loop diuretics, vasodilators, inotropes and opiates, with diuretics as the cornerstone of AHF therapy. These pharmacological treatments are focused on achieving short-term symptom relief and decongestion; none have definitively shown a beneficial impact on either short- or intermediate-term mortality underscoring the significant unmet medical need in the AHF patient population (Hunt et al 2009). At present, there are no Class 1, Level A pharmacologic guideline recommendations for the treatment of AHF.

Serelaxin (H2) is a naturally occurring peptide hormone associated with many of the maternal hemodynamic and renovascular changes that occur in response to pregnancy, such as systemic and renal vasodilation and increases in global arterial compliance (Conrad 2010, Conrad 2011a, Conrad 2011b, Conrad and Shroff 2011). Serelaxin's activity is initiated by binding to its cognate receptor, serelaxin family peptide receptor 1 (RXFP1), which is present in the systemic and renal vasculature as well as in the human heart (Hsu et al 2002). Nitric oxide, endothelial endothelin type B receptor, vascular endothelial growth factor (VEGF) and cAMP act as mediators for the vasodilatory as well as anti-fibrotic and anti-inflammatory effects of serelaxin (Bani et al 1998; Danielson et al 1999; Dschietzig et al 2003). With these pleiotropic effects, serelaxin may benefit HF patients not only through its favorable hemodynamic effects but also via its protective effects on the heart and kidney, leading to potential mortality benefits.

Serelaxin is a recombinant protein identical in structure to the naturally occurring H2 serelaxin. Its efficacy and safety in AHF patients as a continuous intravenous (IV) infusion for up to 48 hours was evaluated in two multicenter, randomized, double-blind, placebo-controlled trials, including 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).

In the RELAX-AHF study, which enrolled 1,161 AHF patients randomized to receive either serelaxin (N=581) or matching placebo (N=580), both in addition to standard-of-care AHF treatment, the 48-hour intravenous infusion of serelaxin produced dyspnea relief as demonstrated by a 19.4% treatment improvement compared to placebo measured over 5 days by visual analogue scale (VAS), representing one of the two primary efficacy endpoints in the study. Serelaxin was administered according to a weight range adjusted dosing regimen at the nominal dose of 30 µg/kg/day. In addition, serelaxin treatment significantly reduced the incidence of WHF episodes through Day 5 and the overall length of index hospital stay, associated with a range of other in-hospital clinical benefits. These clinical improvements were associated with significant improvements in biomarkers with evidence of less end organ damage in serelaxin treated patients (Metra et al 2013). Analysis of all-cause mortality through Day 180 showed fewer deaths with serelaxin, compared to placebo, with a total of 42 (K-M estimate 7.3%) deaths in the serelaxin group compared to 65 (K-M estimate 11.3%) in the placebo group (hazard ratio 0.63, p=0.020). The mortality difference was largely driven by CV death through Day 180 (K-M estimates 9.6% and 6.1%) in placebo and serelaxin groups, respectively, hazard ratio 0.63, p=0.028. These findings support the sustained benefits of serelaxin observed beyond the initial 48 hours of therapy, in which a clinically and statistically significant 37% reduction in both CV and all-cause mortality through Day 180 were seen (Teerlink et al 2013).

Hence, a replicate phase III study with randomization to intravenous administration of serelaxin or placebo within 16 hours of clinical presentation in AHF patients similar to RELAX-AHF trial is proposed to further assess its effect on CV death and other clinical outcomes including all-cause mortality during a follow-up period of 180 days. The CRLX030A2301 protocol describes a multi-center, randomized, double-blind, placebo-controlled, event-driven study which aims to evaluate the efficacy and safety/tolerability of intravenous serelaxin, when added to standard therapy, in AHF patients who present with dyspnea, normal-to-elevated systolic BP and mild-to-moderate renal impairment.

1.2 Purpose

This is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of intravenous infusion of 30 µg/kg/day serelaxin for 48 hours, when added to standard therapy, in approximately 6,375 AHF patients. Efficacy will be determined based on the relative reduction in CV death and other clinical outcomes including all-cause mortality through a follow-up period of 180 days, as compared to placebo. Data from this study is intended to replicate the reduction in mortality in AHF patients observed in the RELAX-AHF trial.

2 Study objectives

2.1 Primary objectives

- To demonstrate that serelaxin is superior to placebo in reducing CV death in AHF patients during a follow-up period of 180 days
- To demonstrate that serelaxin is superior to placebo in reducing worsening heart failure through Day 5.

2.2 Key and other secondary objectives

Key secondary objectives

- To demonstrate that serelaxin is superior to placebo in reducing all-cause mortality during a follow-up period of 180 days
- To demonstrate that serelaxin is superior to placebo in reducing the length of total hospital stay during the index AHF hospitalization
- To demonstrate that serelaxin is superior to placebo in reducing the composite endpoint of CV death or rehospitalization due to heart failure/renal failure, during a follow-up period of 180 days

Other secondary objectives

Efficacy

- To demonstrate that serelaxin is superior to placebo in reducing the length of ICU and/or CCU stay during the index AHF hospitalization
- To demonstrate that serelaxin is superior to placebo in relieving signs and symptoms of congestion through Day 5
- To compare serelaxin to placebo in the changes of selected biomarkers in a subset of randomized patients

Safety

- To evaluate the safety and tolerability of intravenous serelaxin in AHF patients

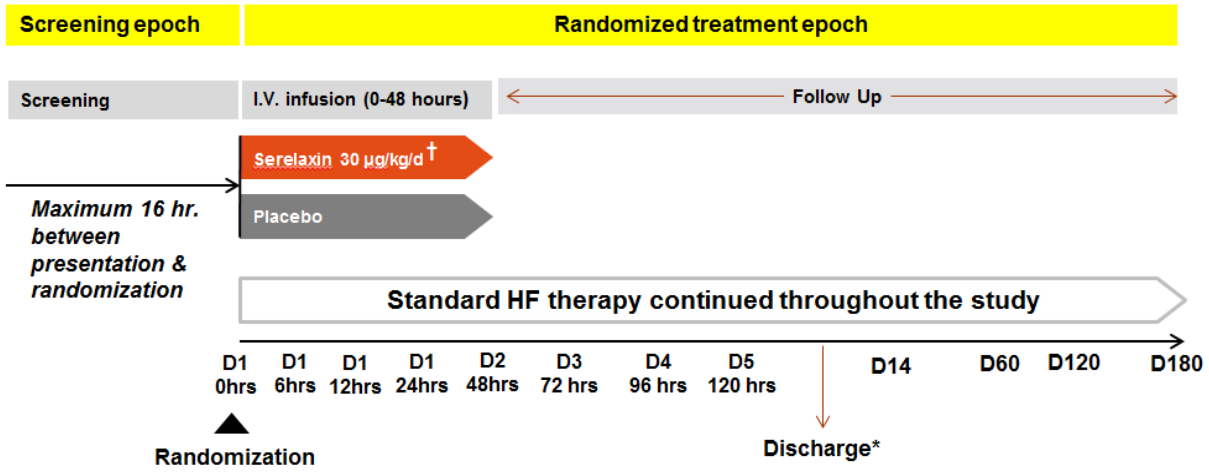
[redacted]

[redacted]

3 Investigational plan

3.1 Study design

Figure 3-1 Study design



- † Weight-range based dosing regimen for serelaxin and matching placebo (see Table 5-3)
- *If Discharge Visit coincides with a scheduled visit, only the Discharge Visit will be performed.
- Presentation starts as the earliest of (1) time of presentation either at the ER/ED, ICU/CCU or ward, (excludes EMS or other pre-hospital care); or (2) time of first IV loop diuretic prior to arrival at the hospital (this includes outpatient clinic, ambulance, or hospital including emergency department) for the treatment of the current AHF episode.

This study is a multicenter, randomized, double-blind, placebo-controlled, event-driven phase IIIb clinical trial designed to evaluate the efficacy and safety of an intravenous infusion of serelaxin when added to standard therapy in AHF patients. After assessing eligibility during the screening period, patients who meet the study inclusion and exclusion criteria will be randomized 1:1 to receive an intravenous infusion of either serelaxin or matching placebo in a double-blind manner for up to 48 hours (Figure 3-1). Potential study candidates are those patients hospitalized for AHF, who have received at least 40 mg intravenous furosemide (or equivalent) prior to screening, with dyspnea at rest or minimal exertion, systolic BP ≥125 mmHg at the time of screening, and mild to moderate renal impairment measured as an estimated eGFR of ≥ 25 and ≤ 75 mL/min/1.73m^2 by sMDRD formula (Levey et al, 2003). These patients must be randomized **within 16 hours** of presentation, (presentation starts as the

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

Serelaxin (and/or matching placebo) will be administered as a continuous intravenous infusion for 48 hours according to a weight-range adjusted dosing regimen at the nominal dose of 30µg/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 patient's systolic BP is decreased by >40 mmHg from baseline but the absolute systolic BP is ≥100 mmHg in two consecutive measurements 15 minutes apart, the study drug infusion rate should be decreased by 50% for the remainder of the infusion period. If the patient's systolic BP falls to <100 mmHg in two consecutive measurements 15 min apart, study drug must be permanently discontinued. 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 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 in Section 6.5.2. If hypotension persists beyond the 5 hours 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 hours post event should be captured in the source documents; only heart rate and blood pressure outlined in Section 6.5.2 will be entered into the eCRFs.

All randomized patients will be assessed daily while hospitalized up to Day 5, at Discharge, and then followed up at scheduled visits for a period of 180 days. Patients discharged prior to Day 5 will return to the hospital/clinic for Day 5 procedures. They are required to receive standard-of-care treatment for HF during both the index hospitalization and post discharge per local and institutional practice guidelines. Visits to assess efficacy are scheduled through Day 5, at Discharge, and Days 14, 60, 120 (telephone contact) and 180. For the safety evaluation, all adverse events (AEs) will be collected from signing of the informed consent form through Day 5 for non-serious AEs and through Day 14 for serious AEs.

In addition to the core study, ECG, laboratory and biomarker substudies will be conducted.

- At least 500 patients from selected centers will participate in an ECG substudy. ECGs will be performed at Baseline and at the end of study drug infusion.
- At least 1600 patients from selected centers will participate in a laboratory substudy. Safety laboratories will be collected at Baseline, daily while hospitalized up to Day 5, Discharge and Day 14. Patients discharged prior to Day 5 will return to the hospital/clinic for Day 5 procedures.
- At least 1600 patients from selected centers participating in the laboratory substudy will also participate in the biomarker substudy. Biomarkers will be collected at Baseline, Days 2, and 5, Discharge, and Day 14. Patients discharged prior to Day 5 will return to the hospital/clinic for Day 5 procedures.

[redacted]

Based on sample size calculations based on RELAX-AHF, approximately 6,800 randomized AHF patients will be required to accrue the number of events during the 180-day follow-up

period necessary to reach the primary efficacy endpoint. Once randomized, all randomized patients will be followed to 180-day.

There will be one interim analysis at 60% of the accrued numbers of confirmed CV deaths (see details in Section 10.6 and Section 10.7). If following the interim analysis, the trial is concluded early for efficacy, all ongoing randomized patients will be followed for 180 days.

3.2 Rationale of study design

This replicate Phase IIIb outcome study in AHF patients is designed as a multicenter, randomized, double-blind, placebo-controlled, event-driven study in order to assess the efficacy, safety and tolerability of intravenous infusion of serelaxin for 48 hours with a weight-range adjusted regimen targeted at approximately 30 µg/kg/day. The AHF patients randomized to either serelaxin or placebo in the study will be followed for a period of 180 days, and are required to receive standard-of-care background HF management during both the index hospitalization and post discharge according to regional or local guidelines/institutional standards.

The primary objective of this study is to further establish that serelaxin is superior to placebo in reducing CV death in AHF patients during the follow-up period of 180 days and in reducing worsening heart failure through Day 5. The reduction in CV death is an efficacy benefit suggested by the Pre-RELAX-AHF study and observed in the completed RELAX-AHF trial. The rate of mortality in AHF remains high despite contemporary standard-of-care management, which has not changed significantly in the last 10 years, and represents a key unmet need for AHF patients.

The reduction in worsening heart failure through Day 5 is a potential efficacy benefit which is evolving among the scientific community as an increasingly clinically relevant treatment goal of AHF. Following initial stabilization, in-hospital WHF occurs in 10- 30% of hospitalized patients reflecting a severe manifestation of the AHF disease continuum requiring immediate intensification of rescue therapy (Torre-Amione et al 2009, Cotter et al 2010, Metra et al 2010a, Teerlink et al 2013) and represents another key unmet need for AHF patients.

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

The weight-range adjusted dose regimen of serelaxin (see Table 5-1 in Section 5.5.4) at the nominal dose of 30 µg/kg/day studied in RELAX-AHF study will be evaluated in this phase IIIb outcome study, and serelaxin will be administrated via continuous intravenous infusion for 48 hours during the most critical early period of AHF patient management to achieve decongestion, hemodynamic improvement and end organ protection. For patients who experience significant systolic BP decrease during the 48-hour study drug infusion, protocol-specified dosing adjustment and/or discontinuation rules must be followed to ensure patient safety (refer details in Section 5.5.5). In the completed 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 safety and tolerability. Importantly, serelaxin provided sustained benefits beyond the initial 48 hours of therapy leading to a clinically and statistically significant 37% reduction in both CV and all-cause mortality through Day 180 (Teerlink et al 2013). 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.

3.4 Rationale for choice of comparator

This placebo-controlled study has been designed to demonstrate the superiority of serelaxin treatment over placebo in the reduction of CV death and other clinical outcomes in AHF patients. There is no evidence based therapy that has been shown to provide a mortality benefit in AHF and thus an active comparator is not available. All patients in this study, however, will be required to receive standard-of-care background HF management during both hospitalization and the follow-up period of 180 days.

3.5 Purpose and timing of interim analyses/design adaptations

There will be one interim analysis at 60% of the accrued numbers of CV deaths using Lan-DeMets spending function of O'Brien-Fleming (OF) stopping boundary which allows early stopping in case of overwhelming evidence of treatment benefit. (See details in Section 10.6 and Section 10.7).

3.6 Risks and benefits

Dyspnea and congestion are the cardinal presenting features of AHF. The rapid onset or change in signs and symptoms of HF requires urgent care. Hospitalization and worsening heart failure with accompanying end organ damage, namely, worsening renal function and myocardial wall stress and injury, are both associated with increased mortality. Although therapies are available to improve dyspnea and congestion in AHF, a substantial number of patients remain symptomatic prior to discharge. Importantly, no AHF therapy to date has demonstrated a mortality benefit.

Serelaxin infused for 48 hours in both the pre-RELAX-AHF (Teerlink et al, 2011) and RELAX-AHF study (Teerlink et al, 2013) demonstrated significant improvement in dyspnea and signs and symptoms of congestion. It was also associated with significant reductions in early worsening heart failure events and length of stay during the index hospitalization including duration of intensive care. Reductions in both cardiovascular and all-cause mortality were observed in the serelaxin-treated patients in RELAX-AHF. Pre-specified biomarker changes suggest serelaxin therapy has a protective effect on both the heart and kidney, supporting the mortality benefit. Serelaxin was generally well-tolerated with no notable differences in the overall adverse event profile compared to placebo. Although blood pressure can decrease in a portion of patients due to the vascular mechanism of action of the drug, worse outcomes were not observed in these patients. The current instructions for the management of systolic blood pressure (SBP), including close and careful monitoring as well as mandatory dose adjustment or stopping rules, which were utilized during RELAX-AHF, support that current safety rules and management of SBP are both robust and sufficient.

The risk to patients participating in study will be minimized by compliance with the inclusion/exclusion criteria and close clinical monitoring, which proved effective during the RELAX-AHF trial. 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 follow-up period of 180 days.

Women of child bearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study. Such participants are required to sign informed consent that outlines the risks as well as protocol specific safety rules to adhere to the contraception requirements for the duration of the study. If there is any question regarding compliance, the patient should not be enrolled.

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

4 Population

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. It is aimed to randomize approximately 6,800 patients [redacted]

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any study-specific assessment is performed*
2. Male or female ≥18 years of age, with body weight ≤160 kg
3. Hospitalized for AHF with the anticipated requirement of intravenous therapy (including IV diuretics) for at least 48 hours; AHF is defined as including all of the following measured at any time between presentation (including the emergency department) and the end of screening:
   - Persistent dyspnea at rest or with minimal exertion at screening and at the time of randomization, despite standard background therapy for acute heart failure including the protocol required intravenous furosemide of at least 40 mg total (or equivalent).
   - Pulmonary congestion on chest radiograph
   - BNP ≥ 500 pg/mL or NT-proBNP ≥2,000 pg/mL; for patients ≥ 75 years of age or with current atrial fibrillation (at the time of randomization), BNP ≥ 750 pg/mL or NT-proBNP ≥ 3,000 pg/mL ***
4. Systolic BP ≥125 mmHg at the start and at the end of screening
5. Able to be randomized **within 16 hours** from presentation to the hospital, including the emergency department**
6. Received intravenous furosemide of at least 40 mg total (or equivalent) at any time between presentation (this includes outpatient clinic, ambulance, or hospital including emergency department) and the start of screening for the study for the treatment of the current acute HF episode. Time from presentation to start of furosemide administration must be less than 6 hours.
7. Impaired renal function defined as an eGFR*** between presentation and randomization of ≥ 25 and ≤75mL/min/1.73m^2, calculated using the sMDRD equation

** Patient assessments of AHF that are per current local institutional/hospital standard protocol or part of routine clinical care are allowed before signing informed consent, and can be used to support patient screening.*

*** 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 prior to arrival at the hospital (this includes outpatient clinic, ambulance, or hospital including emergency department) for the current acute HF episode.*

****Assessed based on local laboratory*

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 due to non-cardiac causes, such as acute or chronic respiratory disorders or infections (i.e., severe chronic obstructive pulmonary disease, bronchitis, pneumonia), 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 or oral steroids (does not include inhaled steroids); need for intubation or the current use of IV or oral steroids for COPD.
3. Patients with blood pressure > 180 mmHg at the time of randomization 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. Clinical evidence of acute coronary syndrome currently or within 30 days prior to enrollment. (Note: 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.)
6. 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
7. Patients with severe renal impairment defined as pre-randomization eGFR < 25 mL/min/1.73m^2 calculated using the sMDRD equation, and/or those receiving current or planned dialysis or ultrafiltration
8. Patients with hematocrit <25%, or a history of blood transfusion within the 14 days prior to screening, or active life-threatening GI bleeding.
9. Known hepatic impairment (as evidenced by total bilirubin > 3 mg/dL, or increased ammonia levels, if performed) or history of cirrhosis with evidence of portal hypertension such as varices.
10. Significant, uncorrected, left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy or severe aortic stenosis (i.e., aortic valve area <1.0 cm^2 or mean gradient >40 mmHg on prior or current echocardiogram), and severe mitral stenosis
11. Severe aortic insufficiency or severe mitral regurgitation for which surgical or percutaneous intervention is indicated.

12. Documented, prior to or at the time of randomization, restrictive amyloid myocardiopathy, OR acute myocarditis or hypertrophic obstructive, restrictive, or constrictive cardiomyopathy (does NOT include restrictive mitral filling patterns seen on Doppler echocardiographic assessments of diastolic function).
13. 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 (endotracheal intubation, mechanical ventilation; intra-aortic balloon pump or any ventricular assist device; hemofiltration, ultrafiltration or dialysis), with the exception of IV furosemide (or equivalent diuretic), or IV nitrates at a dose of ≤ 0.1 mg/kg/hour if the patient has a systolic BP >150 mmHg at the start of screening.
14. Any major solid organ transplant recipient or planned/ anticipated organ transplant within 1 year
15. Major surgery, including implantable devices (e.g. ICD, CRT), or major neurologic event including cerebrovascular events, within 30 days prior to screening
16. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past year with a current life expectancy less than 1 year due to the malignancy.
17. 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 hCG laboratory test
18. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study treatment plus 5 days after cessation of study drug. Highly effective contraception 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 patients 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. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository
  b. 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
  c. Placement of an intrauterine device (IUD) or intrauterine system (IUS)

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

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

19. Use of other investigational drugs within 30 days prior to screening
20. History of hypersensitivity to serelaxin
21. History of participating in serelaxin clinical studies
22. Inability to follow instructions or comply with follow-up procedures
23. Any other medical condition(s) 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 understand and comply with the protocol instructions or follow-up procedures.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

Serelaxin (and/or matching placebo) 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 can be withdrawn from the vials contained in the blinded 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 required for this trial. Nevertheless, patients randomized to either serelaxin or placebo in this study will all be required to receive standard-of-care background HF management during both the index hospitalization and post discharge according to the regional or local guidelines/institutional standard. This treatment can include but is not limited to intravenous and/or oral diuretics, ACE inhibitors/angiotensin receptor antagonists, β blockers, and aldosterone receptor antagonists, etc.

5.2 Treatment arms

Patients will be randomized in a 1:1 ratio to receive continuous intravenous infusion of one of the following treatment assignments for 48 hours:

- Placebo
- Serelaxin (30 µg/kg/day)

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 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 and concealed from patients and investigator staff. 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. 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(s).

The randomization scheme for patients will be reviewed and approved by a member of the IIS Randomization Group.

Misrandomized patients are those who have not been qualified for randomization, have been inadvertently randomized into the study and who did not take study drug. Misrandomized 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 double-blind medication was not administered to the patient. 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 misrandomized into the study.

5.4 Treatment blinding

This will be a double-blind study. Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods:

- Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the exception of the independent unblinded statistician, programmer and data manager/data coordinator (and assistant as required) from an external and independent Data Analysis Center, who need to have access to prepare safety and/or efficacy interim analysis reports for the Data Monitoring Committee (DMC). These personnel will not be involved in any other trial activities.
- The identity of the treatments will be concealed by the use of study drugs that are identical in packaging, labeling, schedule of administration and appearance.
- Unblinding should only occur in the case of patient emergencies (see Section 5.5.10), at the time of interim analysis and at the conclusion of the study. In the event a patient becomes unblinded for any reason other than safety concerns they should continue study treatment and assessments according to the protocol.

- In the event a patient becomes unblinded for safety reasons, they should discontinue study drug and continue study assessments according to protocol.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified by a Patient Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. A center number is also assigned by Novartis to the investigative site. 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. In the electronic data capture (EDC) system, there will be blank CRF books available labeled with a Patient Number. The site should select the CRF book with a matching Patient Number from the EDC system to enter data.

If the patient was inadvertently randomized in the IRT (ie. prematurely randomized even though the patient failed to meet the inclusion/exclusion criteria), and the patient was subsequently not treated, the IRT must be notified immediately that the patient was not treated. The reason for discontinuing from the screening epoch will be entered on the Screening Epoch Study Disposition CRF.

If the patient was correctly randomized in the IRT, but treatment was not administered for any reason, that patient must be followed until Day 180, and all information entered into the appropriate eCRFs.

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with investigational treatment in packaging of identical appearance. Blinded kits will contain 1 vial of serelaxin or placebo, 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.

The investigational treatment packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the 2 treatment arms. On the first day of the infusion, the investigator's staff will identify the investigational treatment package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the medication 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 patient 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 should be stored in a

refrigerator 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 drug and no information about the patient.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.10), at the time of the predefined interim efficacy analyses, and at the conclusion of the study. 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.

5.5.4 Instructions for prescribing and taking study treatment

The study drug infusion will begin after the signing the ICF and the completion of all screening procedures, and continue for 48 hours. Study drug should be administered in a dedicated IV line or port, as soon as possible, but no more than 4 hours after randomization. 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 listed in Table 5-1.

However, there is no restriction for 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. Table 5-2 lists the infusion filters that can be used for this study.

For each randomized patient to receive the study drug according to a weight-range adjusted dosing regimen over a period of 24 hours (Table 5-3), the required amount of study drug will be withdrawn from the 6-mL vials (with 3.5 mL fill) contained in the blinded kits, taking care not to shake the vial, injected into a 250 mL intravenous bag of 5% dextrose solution recommended above, and then infused at a constant rate of 10 mL/hour. 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). The blinded study drug kits, allocated to each randomized patient via IRT, containing one 6-mL vial of serelaxin or placebo (with 3.5 mL fill), will be used to compound study drug for the first 24 hour of infusion for all patients <115 kg in weight; in cases when the subject is ≥115 kg, two study drug kits will be assigned via IRT for the first 24 hour 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.

Table 5-3 Weight-range adjusted dosing regimen of serelaxin (or placebo)

Body weight (kg)	Serelaxin or placebo (mg)	Volume of serelaxin or placebo 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/databased in the IRT.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Table 5-4 describes the actions required for a systolic BP decrease during the period of study drug infusion, which must be strictly followed.

Table 5-4 Dosing adjustment of study drug administration in the event of systolic BP decrease

Changes in systolic BP during infusion*	Adjustments of study drug administration
Decrease >40 mmHg from pre-treatment at baseline, 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 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 systolic 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.

Changes in study drug dose must be recorded on the Dosage Administration Record CRF.

5.5.6 Rescue medication

The investigator may prescribe any medications and/or supportive care during the study based on clinical needs. Any medication and/or supportive care administered must be recorded on the appropriate Concomitant Medications or Tests/Procedures/Treatments CRFs.

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) at any time between presentation to emergency services (this includes outpatient clinic, ambulance, or hospital including emergency department) or hospital and screening for the study.

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, mechanical ventilation, or any ventricular assist device), with the exception of IV furosemide (or equivalent), or IV nitrates at a dose of $\leq$ 0.1 mg/kg/hr if the patient has a systolic BP > 150 mmHg at screening. Use of IV furosemide (40 mg or equivalent) is an inclusion criterion; further doses of IV furosemide can be administered at any time after enrollment.

Major cardiovascular and non-cardiovascular classes of medication taken by a subject approximately 30 days prior to study drug initiation and on a daily basis while hospitalized through Day 5, at Discharge, and at Days 14, 60, 120 and 180 will be recorded. Only those medications currently being taken or that were taken within 24 hours prior to the visit will be collected. These include but are not limited to: loop diuretics, other diuretics, ACE inhibitors, angiotensin receptor antagonists, beta-blocker, hydralazine, nitrates, calcium channel blockers, digoxin, non-steroidal anti-inflammatory agents, COX-2 inhibitors, aminoglycoside antibiotics, inotropes, vasodilators and others (e.g. insulin, oral antidiabetics, statins, anticoagulants etc.).

The investigator may prescribe any additional medications during the study as dictated by the patients' condition. Administration of standard treatment should in no instance be delayed or withheld due to patient's participation in the study. Standard treatment includes, but is not limited to, administration of the major classes of medications, as described above, 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 should instruct the patient to notify the investigator or associated study personnel about any new medications he/she takes after the patient was enrolled into the study.

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 screening. Thus, study drug should 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 dictated by the patients' condition. Administration of standard treatment should never be delayed or withheld due to patient's participation in the study. The investigator should exercise caution when up-titrating or adding concomitant standard therapies that might decrease BP during study drug infusion. Investigator may consider not administering all BP lowering medication simultaneously. Changes to these medications during the index hospitalization should be recorded on the CRF.

5.5.9 Discontinuation of study treatment and premature patient withdrawal

Discontinuation of study treatment: The investigator should 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:

- If the patient's systolic BP falls to <100 mmHg in two consecutive measurements 15 min apart, study drug must be permanently discontinued. Measures may be taken by the investigator to address the decrease in blood pressure during the intervening 15 minutes, if clinically indicated. (see details in Table 5-4)
- Pregnancy
- Any significant risk to the patient's safety

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should be followed per the visit/assessment schedule illustrated in Table 6-1 until the study is complete. If they fail to return for these assessments for unknown reasons, every effort should be made to contact them as specified in Section 5.5.11.

For any patient(s) whose treatment code has been broken inadvertently for any reason, study drug treatment should be continued.

Patient withdrawal: Patients may voluntarily withdraw consent to participate in 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. However, if local regulations permit, sites will be asked to check public registries on a regular basis to try and obtain a health status on their patients, so that the Survival Information eCRF page can be completed.

Patients can also refuse to participate in specific aspects of the study and/or take study medication at any time without withdrawing consent and permission should be requested of the patient to conduct follow-up visits or calls. Investigators should 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 health status and/or mortality information for patients who are unable to or refuse to return for clinic visits.

Lost to follow-up: For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, 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. A patient should not be considered lost to follow-up until just prior to database lock, after every effort to contact the patient has been exhausted.

5.5.10 Emergency breaking of treatment assignment

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Currently, there is no known treatment available to reverse the effect of seralaxin. Consequently, in case of an emergency, management of the emergency condition will be independent from the knowledge of study treatment. If the knowledge of study treatment is deemed absolutely necessary, emergency treatment code breaks will be performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Global Trial Leader (GTL) that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, study treatment name, patient number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the patient in case an emergency treatment code break is required at a time when the investigator and backup are unavailable.

Any patient who is unblinded will continue in the study and complete all study assessments according to the protocol.

5.5.11 Study completion and post-study treatment

Patient participation will be completed 180 days after the start of the study drug infusion.

The investigator also must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.5.12 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated for a prematurely withdrawn patient. 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 IRBs and/or ECs of the early termination of the trial.

It is planned to have one formal interim efficacy analyses. The cut-off for this interim analysis is planned when 60% of the targeted total number of CV deaths is achieved. The trial may be

concluded early for efficacy, at the recommendation of the DMC, if a significant difference between two treatment arms for the number of CV deaths is achieved by crossing the pre-specified boundary at interim analysis.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "X" or "S" when the required assessments and/or procedures are performed at a scheduled study visit. 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 outpatient study visits. Patients unable or unwilling to return to the hospital/clinic for scheduled outpatient visits will be contacted by telephone as close as possible to the expected visit to obtain information about endpoints and survival status.

Patients who prematurely discontinue the investigational treatment remain in the study and should 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 should 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.

Patients eligible to participate in this study must be randomized within 16 hours of presentation. Presentation starts at the earliest of (1) time of presentation either at the ER/ED, ICU/CCU or ward, (excludes EMS or other pre-hospital care); or (2) time of first IV loop diuretic prior to arrival at the hospital (this includes outpatient clinic, ambulance, or hospital including emergency department) for the current AHF episode.

Prospective study candidates will be identified either enroute to or upon arriving at the ED/ER/hospital. After identifying a potential subject, an ICF must be signed before performing study-related screening procedures that are not considered standard of care for AHF patients at that site. Procedures that are part of a site's standard of care for an individual with AHF may pre-date the signed ICF. The AE and SAE reporting period will begin at the time the ICF is signed.

Screening will continue until the patient has been deemed eligible for enrollment and randomized into the study via the IRT.

Table 6-1 Assessment schedule

Epoch	***Screening***	***Randomized Treatment***												
	Screen [d]	**Baseline**	**Study drug infusion[a]**				**Post-treatment daily assessments**				**Follow-up[c]**			
Time points	**Hour -16**	**Hour 0 (Day 1)**	**Hour 6 (Day 1)**	**Hour 12 (Day 1)**	**Hour 24 (Day 1)**	**Hour 48 (Day 2)**	**Hour 72 (Day 3)**	**Hour 96 (Day 4)**	**Hour 120 (Day 5)[b]**	**Discharge[e]**	**Day 14**	**Day 60**	**Day 120**	**Day 180 /PSW**
Visits	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**		**109**	**110**	**111**	**199**
Visit Date	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Demography	X													
Screening disposition	X													
BNP or NT-pro-BNP for study entry	X													
Estimated GFR (sMDRD) for study entry	X													
Chest X-Ray [g]	S													
ECG[q]	S								S	S				
ECG Substudy [n]		X				X								
Medical History – Protocol Solicited Events	X													
Medical History	X													
Heart Failure and Diabetes History	X													
Alcohol History	X													
Drug Abuse History	X													
Smoking History	X													
Pregnancy Test (CHBP females only) [f]	X													
Body Weight[t]	X				X	X	X	X	X	X	X	X		X

Epoch	***Screening***	***Randomized Treatment***												
	Screen [d]	**Baseline**	**Study drug infusion[a]**				**Post-treatment daily assessments**				**Follow-up[c]**			
Time points	**Hour -16**	**Hour 0 (Day 1)**	**Hour 6 (Day 1)**	**Hour 12 (Day 1)**	**Hour 24 (Day 1)**	**Hour 48 (Day 2)**	**Hour 72 (Day 3)**	**Hour 96 (Day 4)**	**Hour 120 (Day 5)[b]**	**Discharge[e]**	**Day 14**	**Day 60**	**Day 120**	**Day 180 /PSW**
Visits	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**		**109**	**110**	**111**	**199**
Height	X													
Echocardiogram[r]		X												
Physical Examination with Vital Signs [h]	S/X	X			X	X	X	X	X	X	X	X		X
BP and HR measurements [i]	X	X	X	X	X	X	X	X	X	X				
Systolic blood pressure decrease event		X	X	X	X	X								
Index Heart Failure Hospitalization		X												
Index Heart Failure Summary										X				
Health Economics – Tests/Procedures/Treatments		X	X	X	X	X	X	X	X	X	X	X	X	X
Physician assessment of HF signs and symptoms[s]		X	X		X[s]	X[s]	X[s]	X[s]	X[s]	X	X	X		
Chemistry[j]	X				X	X	X	X	X	X				
Hematology[j]	X				X	X	X	X	X	X				
Laboratory Substudy – Chemistry[k]		X			X	X	X	X	X	X	X			
Laboratory Substudy – Hematology[k]		X			X	X	X	X	X	X	X			
Laboratory Substudy – Urine Dipstick[K]	S													
Biomarker Substudy [l]		X				X			X	X	X			
Concomitant Medications[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital status and clinical outcome assessments			X	X	X	X	X	X	X	X	X	X	X	X

Epoch	***Screening***	***Randomized Treatment***												
	Screen [d]	**Baseline**	**Study drug infusion[a]**				**Post-treatment daily assessments**				**Follow-up[c]**			
Time points	**Hour -16**	**Hour 0 (Day 1)**	**Hour 6 (Day 1)**	**Hour 12 (Day 1)**	**Hour 24 (Day 1)**	**Hour 48 (Day 2)**	**Hour 72 (Day 3)**	**Hour 96 (Day 4)**	**Hour 120 (Day 5)[b]**	**Discharge[e]**	**Day 14**	**Day 60**	**Day 120**	**Day 180 /PSW**
Visits	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**		**109**	**110**	**111**	**199**
Assessment of readmission											X	X	X	X
Administer study medication		X→	→	→	→	→								
Contact IRT/IWRS		X			X									
Adverse and serious adverse events [m]		X			X	X	X	X	X	X	X			
Follow up completion form														X
Withdrawal of Informed Consent Form[p]	X													X

PSW = premature patient withdrawal; X= assessment to be recorded on clinical database; S= assessment to be recorded on source documentation

[a] Study drug treatment will be administered as continuous intravenous infusion for up to 48 hours. Dosage can be adjusted under specific circumstances as described in Section 5.5.5

[b] Patients discharged prior to Day 5 will return to the hospital/clinic for Day 5 procedures. Patients unable or unwilling to return to the hospital/clinic will be contacted on or after Day 5 by telephone to obtain information about AEs/SAEs, potential endpoints and survival status.

[c] Patients discharged prior to Day 14 will return to the hospital/clinic for Day 14 procedures. Patients unable or unwilling to return to the hospital/clinic will be contacted on or after Day 14 by telephone to obtain information about SAEs, potential endpoints and survival status. The Day 60 and Day 180 assessments will be conducted as outpatient visits if the patient is discharged prior. The Day 180 assessments can be performed as early as - 7 days from the timepoint. The Day 120 assessment will be conducted by telephone. Patients unable or unwilling to return to the hospital/clinic for scheduled outpatient visits will be contacted by telephone as close as possible to the expected visit to obtain information about endpoints and survival status. If a patient fails to return for the remaining outpatient visit(s) the investigator should show “due diligence” by contacting the patient, family or family physician up to the time of database lock.

[d] Procedures performed as part of a site’s standard of care for an individual with AHF can be done during the pre-screening interval and may pre-date the signed ICF.

[e] If Discharge Visit coincides with a scheduled visit, only the Discharge Visit will be performed.

[f] At screening, a locally-analyzed sample will be obtained for female patients of child-bearing potential to qualify the patient for study entry.

[g] Chest X-ray may be interpreted by the study physicians or physicians attending to the patient. Interpretation and the person interpreting the radiograph must be recorded in the source documentation. A radiologist’s interpretation is not necessary for the purposes of the study.

[h] A complete physical will be performed at screening; an abbreviated physical examination will be performed at all other specified timepoints. Following randomization, all physical examinations should be performed daily at approximately the same time of day. Daily vital signs measurements may be made and recorded by trained study personnel as well as trained healthcare personnel as part of their routine clinical duties. The first recorded measurement per day will be used as the daily measurement for that day. Refer to Section 6.5.1.

[i] BP and HR measurements are to be performed at 30 & 60 minutes and then every hour for the first 6 hours of study drug infusion, and then every 3 hours during study drug infusion, 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 until the earlier of Day 5 or Discharge. All measurements should be performed as close as possible to specified timepoints. 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. Refer to Section 6.5.2.

[j] Blood will be locally collected and analyzed daily during hospitalization. If discharge occurs prior to Day 5, local blood collection will not be required at the Day 5 hospital/clinic visit. 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. Refer to Section 6.5.4.

[k] Blood will be collected in a subset of randomized patients participating in the laboratory substudy for measurement of biochemistry, hematology, and plasma HbA1C by the central laboratory. Following randomization, central laboratory collections can be adjusted to conform to the hospital's routine laboratory collection schedule and can be collected at any time of day. Baseline collection can be done at screening at the same time as the local laboratory collections. Urine dipstick will be measured locally at screening to rule out any conditions requiring further diagnostic evaluation or treatment. Refer to Section 6.5.4.3

[l] Blood will be collected in a subset of randomized patients participating in the biomarker substudy to be performed by the central laboratory. Following randomization, biomarker substudy laboratory collections can be adjusted to conform to the hospital's routine laboratory collection schedule and can be collected at any time of day.

Refer to Section 6.6.6

[m] Non-serious AEs and SAEs will be reported from the signing of the ICF through Day 5 and 14, respectively.

[n] ECGs will be collected in a subset of randomized patients participating in the ECG substudy and sent to a central ECG vendor for evaluation. ECGs will be collected at Baseline and at the end of study drug infusion. Refer to Section 6.5.5.

[o] Major cardiovascular and non-cardiovascular classes of medication taken by a subject approximately 30 days prior to study drug initiation and on a daily basis while hospitalized through Day 5, at Discharge, and at Days 14, 60, 120 and 180 will be recorded. Only those medications currently being taken or that were taken within 24 hours prior to the visit will be collected.

[p] Withdrawal of consent form is only completed when a patient does not want to participate in the study any more 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..

[q] ECGs will be performed and interpreted locally at screening and at Day 5 or discharge, whichever occurs first. The ECG interpretation and person interpreting the ECG must be recorded in the source documents

[r] The echocardiogram should be performed as soon as possible post randomization, but prior to discharge. If an echocardiogram is performed during the screening period (i.e. within the 16 hours window) and the patient is subsequently randomized, the screening echocardiogram will qualify as the index hospitalization echocardiogram and a repeat echocardiogram post randomization will not be necessary.

[s] At hours 24, 48, 72, 96 and 120, physician assessment of HF signs and symptoms will include an assessment of the occurrence of worsening heart failure in the interval preceding the visit. These evaluations should be done at approximately the same time of day, each day, in the same position, and hospital/clinic setting, preferably by the same assessor. Refer to Section 6.4.4.

[t] Body weight measurements performed during hospitalization can be performed anytime

6.1 Information to be collected on screening failures

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

For all patients who have signed informed consent and are entered into the next epoch of the study, all adverse events **occurring after informed consent is signed will be** recorded on the Adverse Event CRF.

Investigators will have the discretion to record abnormal test findings on the medical history CRF 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, weight and height. Relevant medical history/current medical condition data includes data until the start of study drug. 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.

6.3 Treatment exposure and compliance

Study drug will be given IV under medical supervision. Infusions times and rates will be recorded in the CRF. Study drug and supplies must be made available for inspection by the clinical trial monitor for accountability.

6.4 Efficacy

6.4.1 Efficacy assessment 1

- The primary efficacy endpoint is defined as the time to confirmed CV death during a follow-up period of 180 days.
- Time to first occurrence of worsening heart failure* through Day 5 (considering death in the 5-day period as WHF event)

** Worsening heart failure 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 ventilatory, renal or circulatory support. Such treatment can include the institution or up-titration of IV diuretic, IV nitrates or any other IV medication for heart failure, or institution of mechanical support such as mechanical ventilation, ultrafiltration, hemodialysis, intra-aortic balloon pump or ventricular assist device, etc. WHF can occur either during the index admission, or after discharge as an unplanned rehospitalization or unscheduled physician office/emergency department visit due to a primary diagnosis of HF.*

This endpoint also includes patients who die in this 5-day period of any cause before experiencing episode(s) of WHF.

6.4.2 Efficacy assessment 2

Key secondary efficacy endpoints will comprise:

- Time to all-cause death during a follow-up period of 180 days
- Length of total hospital stay for the index AHF hospitalization
- Time to first occurrence of the composite endpoint of CV death or rehospitalization due to heart failure/renal failure, during a follow-up period of 180 days.

Other secondary efficacy endpoints will comprise:

- Length of ICU and/or CCU stay for the index AHF hospitalization
- Change from baseline in congestive signs and symptoms of HF through Day 5
- Change from baseline in selected biomarkers from baseline through Day 14 in a subset of randomized patients

6.4.3 Appropriateness of efficacy assessments

The primary efficacy endpoint is defined as the time to confirmed CV death during a follow-up period of 180 days. Mortality in AHF patients remains high despite contemporary standard-of-care HF management, and CV death is a well-established efficacy endpoint to assess the effect of pharmacologic interventions on clinical outcomes of HF patients. The follow-up period of 180 days is selected here based on the finding in completed RELAX-AHF study that sustained benefits beyond the initial 48 hours of serelaxin therapy were associated with a clinically and statistically significant 37% (95% CI 4-59%) reduction in CV death through Day 180.

6.4.4 Other efficacy assessments

6.4.4.1 Assessment of AHF signs and symptoms

The investigator or appropriately qualified designee will evaluate the signs and symptoms of heart failure, including patient's dyspnea on exertion or at rest, orthopnea, rales, jugular venous pulse (JVP), peripheral edema, and the patient's assessment of dyspnea (Refer to Section 16 Appendix 3). These evaluations will be done at baseline, 6, 24 and 48 hours from start of study drug infusion, and then daily while hospitalized through Day 5, at Discharge, and Days 14 and 60. These evaluations should be done at approximately the same time of day, each day, in the same position, and hospital/clinic setting, preferably by the same assessor. To ensure consistency, if the same assessor cannot perform the daily assessments, the second assessor should evaluate the patient together with the first assessor at least once prior to performing the assessments independently.

6.4.4.2 Rehospitalization

Rehospitalization will be defined as all unplanned hospitalization (including admission to a hospital or any attendance in an acute care setting e.g. ED, or in another health care facility) of 24 hours or greater, regardless of whether the patient was admitted to the hospital.

6.5 Safety

6.5.1 Physical examination

An overall physical examination will be performed by the investigational staff at screening and include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. An abbreviated physical examination will be performed at all other visits and include the examination of general appearance and vital signs (SBP/DBP and pulse).

Following randomization, all physical examinations should be performed daily 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 made after signing the informed consent, up to and including Day 5, which meet the definition of an adverse event (AE) must be recorded on the Adverse Event section of the eCRF (Section 7.1). Significant findings made after signing the informed consent, up to and including Day 14, which meet the definition of a serious adverse event (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) faxed within 24 hours after awareness of the SAE.

6.5.2 Vital signs

Body temperature, blood pressure, heart rate and respiration rate will be measured at Screening, Baseline, daily while hospitalized up to Day 5 and at Discharge, and Days 14, 60 and 180. Daily measurements may be made and recorded by trained study personnel as well as trained healthcare personnel as part of their routine clinical duties. The first recorded measurement per day will be used as the daily measurement for that day.

Patients discharged prior to Day 5 will return to the hospital/clinic for Day 5 procedures. Patients unable or unwilling to return to the hospital/clinical for the Day 5 procedures will be contacted by telephone.

Continuous BP and HR measurements will also be performed at Screening, Baseline, throughout study drug infusion at 30 & 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 until the earlier of Day 5 or discharge. 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.

Should the study drug dose be decreased or the study drug be discontinued prematurely due to blood pressure decrease, then 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.

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, Days 1-5, Discharge, and Days 14, 60 and 180. Measurements performed during hospitalization can be performed anytime.

If patient's body weight cannot be measured at Screening because of the patient physical condition, a verbal weight will be acceptable. Weight should be obtained as soon as the patient is physically able.

6.5.4 Laboratory evaluations

A local laboratory will be used for analysis of all specimens collected. The laboratory name and value must be entered into the eCRF page. Local laboratory specimens will be collected at Screening, daily while hospitalized up to Day 5 and at discharge. 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.

In addition to the local laboratory collections outlined above, at least 1600 patients from selected centers will participate in a laboratory substudy. A central laboratory will be used for the analysis of all baseline and post-baseline specimens collected in the subset of patients participating in the laboratory substudy. Central laboratory specimens will be collected at baseline (can be collected at screening), daily while hospitalized up to Day 5, at Discharge, Day 5 if discharged prior to Day 5, and Day 14. Following randomization, central laboratory collections can be adjusted to conform to the hospital's routine laboratory collection schedule and can be performed at any time of day. Details of the substudy are described in Section 6.5.4.3.

6.5.4.1 Hematology

The following hematology tests will be measured locally at screening and daily during hospitalization: hemoglobin, hematocrit, and white blood cell count, including differential.

6.5.4.2 Clinical chemistry

The following serum chemistry tests will be measured locally at screening and daily during hospitalization: sodium, potassium, glucose, blood urea nitrogen (BUN) or urea, AST, ALT,

alkaline phosphatase, total bilirubin, and creatinine. In addition, BNP/NT pro-BNP and hemoglobinA1c will be measured at screening only.

6.5.4.3 Laboratory substudy

At least 1600 patients from selected centers will participate in a laboratory substudy. All patients at a selected center will be asked to participate in the substudy until all 1600 patients have been enrolled. All patients enrolled in the laboratory substudy will have the substudy blood samples collected in addition to the local laboratory blood samples outlined in Sections 6.5.4.1 and 6.5.4.2 and biomarker blood samples outlined in Section 6.6.6. A central laboratory will be used for the analysis of all baseline and post-baseline specimens collected in the subset of patients participating in the laboratory substudy. All laboratory results (excluding biomarker results) will be communicated by the central lab to the investigators and the sponsor. Details on the collections, shipment of samples and reporting of results by the central laboratory for the patients in the aforementioned substudy are provided to investigators in the laboratory manual.

The following tests will be measured by the central laboratory in the subset of at least 1600 patients participating in the laboratory substudy:

- Hematology: hemoglobin, hematocrit, red blood cell count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), white blood cell count with differential, and platelet count
- Chemistry: *serum* creatinine, blood urea nitrogen, total bilirubin, AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH) sodium, potassium, chloride, calcium, phosphorous, glucose, total protein, albumin, cholesterol, triglycerides and uric acid. Hemoglobin A1c will be performed at baseline only on whole blood.
- Urine dipstick will be measured locally at screening to rule out any conditions requiring further diagnostic evaluation or treatment. Results are to be recorded in the patient's chart.

Since results of substudy related laboratory assessments will be delayed because of sample transit times, local laboratory evaluations will also be performed by the investigators at the site and used to guide patient management (refer to Sections 6.5.4.1 and 6.5.4.2).

6.5.5 Electrocardiogram

6.5.5.1 Local ECGs

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

6.5.5.2 ECG substudy

At least 500 patients from selected centers will participate in a substudy to evaluate the impact of serelaxin on ECGs values. All patients at a selected center will be asked to participate in the substudy until all 500 patients have been enrolled. A standard triplicate 12-lead ECG will be performed at baseline and at the end of study infusion and sent to a central ECG vendor for interpretation. Each ECG tracing should be labeled with the study and patient number, patient

initials (if applicable), date, and kept in the source documents at the study site. Clinically significant abnormalities should also be recorded on the Medical History/Adverse event CRF page.

6.5.6 Pregnancy and assessments of fertility

At screening, a locally-analyzed urine pregnancy test will be performed for all females of childbearing potential. Any subject with a positive pregnancy test at Screening will be excluded from participating in the study.

6.5.7 Appropriateness of safety measurements

The safety assessments selected for this trial are standard assessments for demonstrating safety in this patient population.

6.6 Other assessments

6.6.1 Echocardiogram

An echocardiogram will be performed during the index hospitalization. The echocardiogram should be performed as soon as possible post randomization, but prior to discharge. If an echocardiogram is performed during the screening period (i.e. within the 16 hours window) and the patient is subsequently randomized, the screening echocardiogram will qualify as the index hospitalization echocardiogram and a repeat echocardiogram post randomization will not be necessary.

6.6.2 Resource utilization

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

At Visit 1 (screening), prior heart failure hospitalizations, relevant medical conditions and therapies, and prior procedures will be collected. Throughout the index hospitalization, the level of health care resource utilization will be assessed by the overall length of stay, length of time in specific inpatient care units, and procedures rendered during hospital stay. The frequency and duration of subsequent inpatient hospitalization will be recorded along with the primary reason for the hospital admission and discharge, length of time in specific inpatient care units, and procedures rendered. The frequency of urgent care for AHF lasting more than 24 hours and the procedures rendered will also be recorded.

All attempts will be made to collect RU variables in all patients throughout the duration of the study in order to avoid selection bias. There may also be circumstances when the collection of such data after completion of the study may be warranted.

6.6.3 Health-related Quality of Life

Health related quality of life assessments will not be collected in this study.

6.6.4 Pharmacokinetics

No formal pharmacokinetic analyses will be performed.

6.6.5 Pharmacogenetics/pharmacogenomics

Pharmacogenetics will not be performed in this study.

6.6.6 Other biomarkers

At least 1600 patients from selected centers participating in the laboratory substudy will also participate in the biomarker substudy. All patients at a selected center will be asked to participate in the substudy until all 1600 patients have been enrolled. All patients enrolled in the biomarker substudy will have biomarker blood samples collected in addition to the local laboratory blood samples outlined Sections 6.5.4.1 and 6.5.4.2 and substudy laboratory blood samples outlined in Section 6.5.4.3. Following randomization, biomarker substudy laboratory collections can be adjusted to conform to the hospital's routine laboratory collection schedule and can be collected at any time of day. Biomarkers related to cardiac and renal function/injury will be obtained from blood in the subset of patients participating in the biomarker substudy. Biomarkers will be used to elucidate the effect of serelaxin and to explore drug effect versus baseline biomarkers of risk. Biomarkers of potential interest are high sensitivity troponin T, NT-proBNP, Galectin 3, ST2, Cystatin C and NGAL. This list of potential biomarkers may be changed or expanded further as it is recognized that more relevant or novel biomarkers may be discovered. Biomarkers may be measured during the process of this study or after its completion. Detailed sample handling instructions will be provided in a separate laboratory manual.

7 Safety monitoring

7.1 Adverse events

An adverse event (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. In this study, non-serious AEs will be collected through Day 5, serious adverse events (SAEs) will be collected through Day 14.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may 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 adverse events 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.

Unexpected, 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

patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for labs and other test abnormalities are included in Section 14 Appendix 1.

Adverse events with an onset up to and including Day 5 should be recorded in the Adverse Events CRF 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 discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment (no/yes),
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE)
- action taken regarding study 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; or unknown)

An SAE is any adverse event (appearance of or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(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 through Day 14 and have special reporting requirements; see Section 7.2.

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

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study 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's Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications (IN). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must 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 and through Day 14 must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced *after* Day 14 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 should 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 treatment, 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 number 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 should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

Follow- up information provided should 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 should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is unexpected, i.e., the event is not previously documented as 'expected' in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study drug, this event is considered a **Suspected Unexpected Serious Adverse Reaction (SUSAR)**. A DS&E Department associate may then urgently require further information from the investigator for Health Authority reporting. In general, it is Novartis policy to unblind SUSARs for regulatory reporting. If the unblinding shows that the Novartis drug is involved, Novartis will report this SUSAR in an expedited timeframe (7 or 15 days) to the competent authorities and relevant Ethics Committees (ECs) in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries. In addition, an IN will be issued to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported.

Study-specific unblinding 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 unblinded for expedited reporting to competent authorities/relevant ECs and investigators. In such cases, regulations allow an exemption from SUSAR unblinding and expediting aimed at ensuring the validity of an outcome study (European Commission ENTR/CT13 Guideline 2006; FDA Guidance 2012). Therefore, the rules for unblinding SUSARs during the 14-day SAE collection period will be applied as follows.

1. Endpoint events that will not be unblinded

A SUSAR will not be unblinded, if the event is considered consistent with one of the efficacy endpoints: *Non-CV death, CV death, WHF, rehospitalization due to HF and/or RF.*

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 as blinded reports. INs will not be issued for these events.

2. Endpoint events that will be unblinded

There is a subset of SAEs, which will require unblinding and 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 unblinding 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 Day 14, respectively, SUSARS considered consistent with the following SAE Preferred Terms will not be unblinded and reported in an expedited timeframe to regulatory agencies, ECs or investigators during the course of the study:

> abdominal pain, acute coronary syndrome, acute pulmonary oedema, anaemia, angina pectoris *, anxiety, arthralgia, asthenia, azotaemia, back pain, blood creatinine *, blood pressure *, blood urea nitrogen *, bronchitis *, cardiac arrest, cardiac arrhythmias (all Preferred Terms 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, oedema, oedema due to cardiac disease, oedema peripheral, osteoarthritis, pain in extremity, pericardial effusion, pleural effusion, pneumonia *, presyncope, pulmonary hypertension, pulmonary oedema, 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 as blinded reports. INs will not be issued for these events.

Monitoring of safety data by the Data Monitoring Committee

An external independent Data Monitoring Committee (DMC) (Section 9.4) 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 endpoint and SAE data throughout the trial in a semi-unblinded manner. 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 Novartis to HAs, ECs and investigators within an appropriate timeframe.

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 are both leading to hepatocellular hypoxia; additionally PaO2 alterations can add to the hepatic injury. These events present both acutely with cardiac decompensation events and chronically 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 liver events has to be followed.

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),** are divided into two categories:

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 15-1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger of liver event **without apparent cardiac decompensation as the underlying cause** and as defined in Table 15-1 of Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 15-2 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 is 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 liver event which needs to be followed until resolution.

It is the investigator's responsibility to investigate the potential occurrence of these events. These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded on appropriate CRF pages, including the liver event overview CRF pages.

8 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 should 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 study treatment

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

9 Data review and database management

9.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs 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 CRFs, 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 CRFs 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 CRF 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 CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

9.2 Data collection

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. 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 copies of the patient data for archiving at the investigational site.

9.3 Database management and quality control

Novartis staff review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples, from the laboratory substudy, will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

ECG tracing, from the ECG substudy, will be processed centrally and the results will be sent electronically to Novartis.

Randomization codes and data about all study drug(s) dispensed to the patient will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

9.4 Data Monitoring Committee

An external and independent Data Monitoring Committee (DMC) will be formed for this study to primarily evaluate the unblinded results of pre-specified safety interim analyses of the data during the course of study, which will be provided by an independent and external Statistical Data Analysis Center. This includes interim analyses from entire study population as well as subgroups of interest. In addition, DMC will review efficacy data from one pre-specified interim efficacy analysis when approximately 60% of confirmed CV deaths occurred.

Pending the outcome of the DMC's review from each of the interim analyses, modifications of the study may be made to patient inclusion/exclusion criteria, assessment schedule, etc. Any major recommendation from the DMC will be provided in writing to the Executive Committee and must be reviewed and ratified by the Executive Committee prior to its enactment.

The membership of the DMC and the responsibilities of the DMC and Novartis will be defined in a separate document entitled the 'Data Monitoring Committee Charter'. The DMC Charter will include information about data flow, purpose and timing of DMC meetings, guidance in the decision making process, communication strategy, procedures for ensuring confidentiality, procedures to address conflicts of interest and statistical monitoring guidelines.

9.5 Adjudication Committee

An external and independent Clinical Event Committee (CEC) will review and adjudicate all deaths and rehospitalizations that occur through Day 180 for endpoint determination. The CEC will be responsible for classifying all death events (e.g., CV and non-CV death) and for determining whether pre-specified endpoint criteria were met for rehospitalization due to heart failure or renal failure. The detailed definitions of the endpoints, required documentation, and the adjudication process will be provided to all sites in a separate CEC Manual.

10 Data analysis

10.1 Analysis sets

The following analysis populations will be defined for statistical analysis:

- **Randomized (RAN) set -** All patients who received a randomization number, regardless of receiving trial medication.
- **Safety set (SAF) -** All patients who received any amount of study drug and 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. Patients who receive any amount of serelaxin will be included in the serelaxin treatment group.

- **Full analysis set (FAS) -** All patients in the RAN population who were not misrandomized patients*. Following the intent-to-treat (ITT) principle, patients are analyzed according to the treatment they have been assigned to at the randomization.
- Misrandomized patients are those who have not been qualified for randomization, have been inadvertently randomized into the study and who did not take study drug. Misrandomized 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 double-blind medication was not administered to the patient. These patients should subsequently be discontinued from the study.
- **Per protocol set (PPS)** – all patients in the FAS who received any amount of study medication and have no major protocol deviations (as defined in VAP module 3).

10.2 Patient demographics and other baseline characteristics

Subject demographics (age, sex, ethnicity, race, weight and height) and baseline characteristics will be summarized for the RAN and FAS. Screening BNP, NT pro-BNP and estimated eGFR, laboratory values as reported by the investigator will be summarized with standard descriptive statistics. The number and percentages of patients meeting all eligibility criteria at screening will also be provided. The number and percentage of patients who were hospitalized for heart failure in the past year and patients on IV nitrates at the time of randomization will both be presented. Inclusion and exclusion criteria violations will be listed. Medical history data will be summarized by treatment group. Continuous variables will be summarized using n, mean, median, standard deviation, minimum, maximum, and categorical variables will be summarized using frequency and percentage.

Treatment groups will be compared using the Chi-square test for categorical variables or using t-test for continuous variables. The p-values will be provided for descriptive purpose and 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.

10.3 Treatments

Overall study drug administration details will be summarized for the RAN population. This will include time from presentation to randomization (hrs), time from randomization to study drug administration (hrs), study drug administered (yes/no), reason study drug not administered, actual study drug received, and the number of days infused (one or two). Study drug administration will also be summarized in the Safety Set. The duration of study drug administration (in hours) and the total volume of study drug administered (estimated from the total time and rate of infusion) will be summarized. In addition, the number of patients whose study medication dose was lowered or discontinued prematurely, and the reasons for discontinuation, will be summarized by treatment group.

Concomitant medications and significant non-drug therapies, prior to and after the randomization date, respectively, will be summarized by therapeutic class, preferred term, and treatment group for the randomized population.

10.4 Analysis of the primary and key secondary variable(s)

The primary analysis and the analyses of all secondary and exploratory efficacy variables will be based on the FAS, following the intention-to-treat principle.

10.4.1 Variable(s)

The primary efficacy variables will be the time to confirmed CV death during the follow-up period of 180 days and time to worsening heart failure through Day 5 (considering death in the 5-day period as WHF event).

10.4.2 Statistical model, hypothesis, and method of analysis

CV death

Time-to-event is computed as the number of days from randomization to CV death. Patients without an event will be censored at the earlier of the last date at which the vital status was known or Day 180. Patients who die from a non-cardiovascular cause before Day 180 will be censored at the time of death.

The statistical hypothesis is:

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

The hypothesis will be tested based on the FAS with a logrank test at an initial significance level of $(4/5)\alpha$ within a sequentially rejective multiple testing procedure described in detail in Section 10.5.1. Note that the significance level for the final test will be adjusted to account for the planned interim analysis.

Number and percentage of patients who died from cardiovascular reasons based on the number of patients in the population as denominator will be provided by treatment group. 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.

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.

The SAS procedures PHREG and LIFETEST will be used to conduct the analyses *[SAS/STAT User's Guide, version 9.3]*.

WHF

Time to worsening heart failure through Day 5 will be analyzed using Gehan's generalized Wilcoxon test at an initial significance level of (1/5)α within a sequentially rejective multiple testing procedure described in detail in Section 10.5.1.

Number and percentage of patients who experienced WHF based on the number of patients in the population as denominator will be provided by treatment group. 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.

Kaplan-Meier curves will be presented graphically by treatment group and Kaplan-Meier estimates for selected time points with 95% confidence intervals will be tabulated.

The SAS procedures PHREG and LIFETEST will be used to conduct the analyses *[SAS/STAT User's Guide, version 9.3]*.

10.4.3 Handling of missing values/censoring/discontinuations

A patient without an event will be censored for CV death at the earlier of:

- Date of death for non-CV related causes
- The last date at which the vital status was known
- Day 180

A patient without a WHF event will be censored at the earlier of the last contact date, withdrawal of consent date or 120 hours after randomization.

10.4.4 Supportive analyses

In addition to the primary analyses, the primary efficacy variable, CV death and WHF will also be analyzed using the same primary analysis model on the Per Protocol set as supportive information. Subgroup (age [65 and 75 cut off], gender, race, region, PEF/REF, naïve vs prior history of HF) analyses will be analyzed for both primary endpoints for FAS.

The survival function for each treatment arm will be estimated by the Kaplan-Meier-technique and the Kaplan-Meier curves will be presented for both FAS and PP. The proportion of patients with a primary endpoint will be estimated from the Kaplan-Meier curve for each treatment.

Sensitivity analyses will also be performed using a modified definition of WHF, for example where both signs and symptoms are present.

10.5 Analysis of secondary variables

10.5.1 Efficacy variables

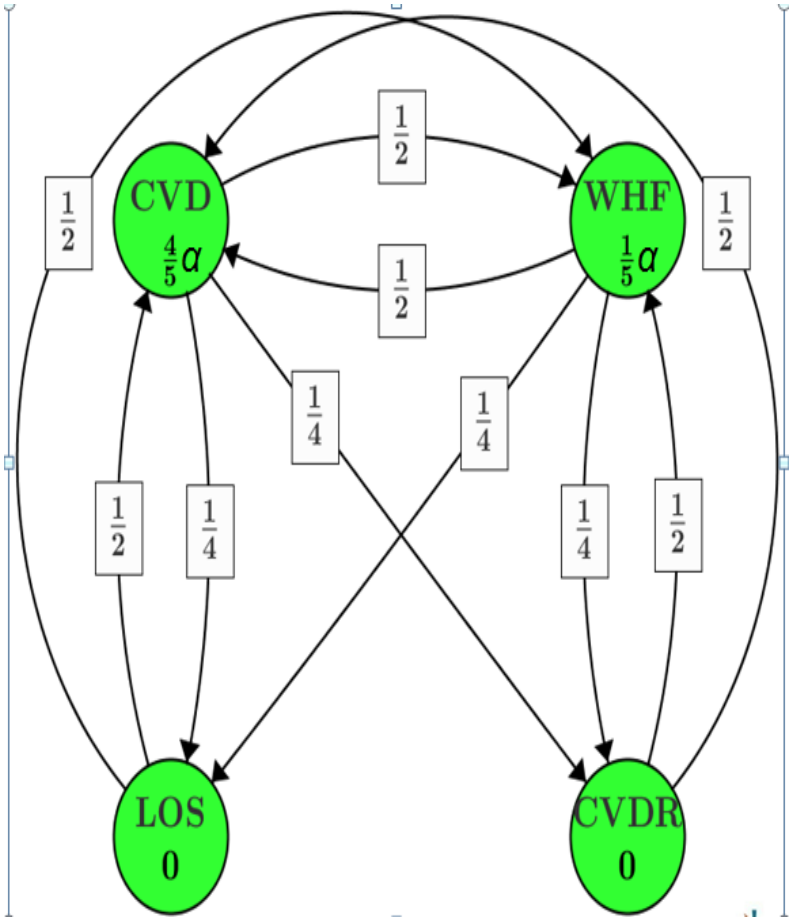
There are three key secondary efficacy variables defined in this study:

- Time to all-cause death through Day 180
- Length of total hospital stay (LOS) during the index AHF hospitalization
- Time to first occurrence of the composite endpoint of CV death or rehospitalization due to heart failure (HF)/renal failure (RF) through Day 180

The key secondary efficacy endpoint of all-cause mortality through Day 180 will not be formally incorporated in a multiple testing procedure. It will be tested with a full α (two-sided) by itself if one or both of the primary endpoints, CV death or WHF is statistically significant.

The other two key secondary variables will be tested using a sequentially rejective multiple testing procedure in testing LOS and composite of CV death or rehospitalization due to HF/RF (CVDR) in controlling overall α (Bretz, et al 2009). Figure 10-1 illustrates this multiple testing procedure for two primary and two key secondary variables with strong control of overall α level of 5%. Note: although CV death will be tested initially at 0.02 (one-sided) significance level and WHF at 0.005 (one-sided) significance level, the final significance level for CV death and WHF will be updated according to the graphical testing strategy incorporating two secondary variables, LOS and CVDR, as depicted in Figure 10-1.

Figure 10-1 Sequentially rejective multiple testing procedure for two key secondary efficacy variables



Where CVD is CV death, WHF is worsening heart failure, LOS is length of hospital stay, and CVDR is CV death or rehospitalization due to heart failure or renal failure.

The time-to-event (from randomization to the event) analysis similar to the primary analysis of CV death will be used for the analyses of all-cause death at Day 180, and composite of CV death or rehospitalization due to HF or renal failure at Day 180. Patients without an event will be censored at the earlier of the last contact date or Day 180.

Length of stay will be defined as the index hospitalization discharge date and time minus the randomization date and time. Patients still in the hospital at Day 60 will be censored at Day 60. Patients who die during the initial hospitalization will be assigned the maximum length of stay (including those censored at Day 60) + 1 day. Treatment groups will be compared using a Wilcoxon rank sum test.

Other secondary efficacy variables will comprise:

- Length of ICU and/or CCU stay for the index AHF hospitalization
- Change from baseline in congestive signs and symptoms of HF through Day 5
- Change from baseline in selected biomarkers from baseline through Day 14 in a subset of randomized patients

The length of ICU and/or CCU stay for the index AHF hospitalization will be analyzed similarly to the length of hospital stay. Change from baseline in congestive signs and symptoms of HF through Day 5 (Section 16 Appendix 3) will be analyzed by displaying the percentage of patients (with asymptotic 95% CIs) by treatment and time points for each of the signs and symptoms variables. A time-to-event (response defined as >=1 point improvement from baseline) analysis will be applied to provide treatment comparisons. Hazard ratios (serelaxin/placebo) of being a responder for each of the signs and symptoms variables will be estimated using a Cox regression model stratified by region with treatment as a factor. Detailed biomarker analyses will be included in the biomarker substudy protocol.

10.5.2 Safety variables

The incidence of AEs recorded through Day 5 and the incidence of SAEs recorded through Day 14 will be presented for the Safety Set. Incident AEs will be considered those AEs with an onset date and time *after* the initiation of study drug. Adverse events with an onset between informed consent and study drug initiation will be listed separately. Adverse events will be coded using the most current version of MedDRA. All reported AEs will be summarized by system organ class (SOC) and preferred term by treatment groups. Serious AEs (SAEs) will be summarized similarly.

In addition, AEs will be summarized by time period of onset: from study drug initiation to Day 5, or from Day 6 to Day 14. 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, and study-drug-related SAEs, SAEs with an outcome of death, and SAEs leading to study drug discontinuation will be summarized by percentages and

frequencies. Percentages will be based on the number of patients in the Safety Set. For the analysis by time period of onset, the percentages will be based on the number of patients in the Safety Set with the corresponding AE form completed.

Laboratory data will be summarized by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), summary statistics of raw data and change from baseline (means, medians, standard deviations, 1st and 3rd quartiles, Q_1 and Q_3) and by flagging of notable values in data listings.

For vital signs, descriptive statistics will be provided for values and change from baseline at each assessment time point for pulse, respiratory rate, body temperature, and weight. Treatment groups will be compared for changes from baseline using t-tests.

The number and proportion of patients who experience a confirmed blood pressure decrease event during study drug administration will be provided. Among patients who experience a confirmed blood pressure decrease event, the events will be further characterized. Summaries will be provided separately for those confirmed events 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.

10.5.3 Resource utilization

Summary statistics will be provided by treatment group on hospital length of stay (total and per ward) for the initial and subsequent hospitalizations, as well as procedures rendered during these hospitalizations,. Additional information will be provided in the Statistical Analysis Plan.

10.5.4 Health-related Quality of Life

Health related quality of life assessments will not be collected in this study.

10.5.5 Pharmacokinetics

Pharmacokinetics will not be collected in this study.

10.5.6 Pharmacogenetics/pharmacogenomics

Not applicable.

10.5.7 Biomarkers

Biological markers will be measured in a subset of patients. Summary statistics for the baseline values, the post-baseline values, and the change from baseline will be provided by treatment group for the FAS and Safety Set.

10.5.8 PK/PD

Not applicable.

10.6 Interim analyses

It is planned to establish an external and Independent Data Monitoring Committee (DMC) to monitor patient safety data on a regular basis during the course of the study. For this study, it is likely DMC will review safety data in a regular frequency, e.g., every six months. DMC may request additional safety data review. Such safety analyses do not inflate the type I error for the primary efficacy hypothesis testing and thus require no multiplicity adjustments.

It is planned to have one formal interim efficacy analyses. The cut-off for this interim analysis is planned when the information fraction (number of confirmed CV deaths relative to the targeted total number of confirmed CV death at the study completion) of 60% is achieved. Some adjustment to the time of interim analysis may be made to coincide with the regular DMC meetings. One-sided tests will be performed and appropriate statistical adjustments for the interim analysis actually performed will be made to ensure the overall one-sided type I error of 0.02 (Lan-DeMets spending function to match an O'Brien-Fleming stopping boundary). For the interim analysis, the analysis dataset will comprise all patients who were randomized before the cut-off date.

The trial may only be concluded early for efficacy, if a significant difference between two treatment arms for the number of CV deaths is achieved by crossing the pre-specified boundary (irrespective of WHF results) at interim analysis and the overall risk/benefit profile is considered positive. Interim analysis will be performed by an external independent statistician at an external data analysis center, who will not be involved in the study conduct. The results will be reviewed by the independent DMC. Investigators and others who are involved in the conduct of the trial and in the analysis of the final trial results, or who have contact with study centers, will remain blinded to the treatment codes and interim analysis results until all monitoring decisions have been made and the database has been locked for final analysis.

Additional details of the interim analysis plan for efficacy and safety will be described in the DMC charter.

10.7 Sample size calculation

The alpha (α) level of 5% is split to CV death at 4% and to WHF at 1%. The sample size calculation is based on the CV death endpoint. This is an event-driven trial with fixed maximum duration of 180 day follow-up period for each patient. In the sample size calculation, the 180-day CV death rate is assumed to be 9.0% in the placebo group, which is about 80% of 11.3% of all cause death observed in the placebo group in the RELAX-AHF study. [redacted] This sample size accounts for one planned efficacy interim analysis when 60% of CV deaths have been accrued, using the Lan-DeMets spending function and an O'Brien-Fleming (OF) stopping boundary.

The interim analysis will be performed when 329 CV deaths are accrued. At the interim analysis, if Z-score of 2.786 (one-sided nominal p = 0.0027) is observed, which corresponds to HR of 0.735 (at least 26.5% RRR), the DMC may recommend to stop the study due to crossing the boundary. If there is no stopping at the formal efficacy interim analysis, the final analysis will need to have a Z-score of 2.072 (one-sided nominal p = 0.0192), which corresponds to HR

of 0.838 (at least 16.2% RRR), to declare a significant study. (East ® 5.4.2, Cytel Inc., Cambridge MA, 2010).

If the observed overall event rate of the CV death endpoint during the course of the trial is much lower than expected based on the design assumptions (assessed on a blinded basis), adjustments may be made to the number of patients to be randomized in order to achieve the required number of events in the pre-planned timeframe (180 days) and thus to preserve the target study power.

For the sample size of 6,800, the unconditional power for the WHF endpoint and all three key secondary endpoints under various HRs (mean difference for Length of Stay) are summarized below in Table 10-1 and Table 10-2:

Table 10-1 Assumed effect sizes for worsening heart failure and the key secondary efficacy variables on power calculation

	Assumed HR or mean difference
Worsening Heart Failure (placebo rate: 12.2%)	0.70
	0.80
All cause death (placebo rate: 11.3%)	0.80
	0.816
	0.83
Length of Stay (mean ±SD between placebo and serelaxin: 0.9 ±9.6 day)	0.9 day
	0.7 day
CV death or HF/RF rehospitalization (placebo rate: 34.1%)	0.85
	0.88

Note: Assumed placebo rates for all cause death and WHF and mean difference (mean ± SD) in LOS between serelaxin and placebo were based on RELAX AHF study; placebo event rate of CV death or HF/RF rehospitalization was estimated to be 34.1% by assuming an exponential distribution with the same hazard as that observed through Day 60 in RELAX AHF study.

Table 10-2 Powers (unconditional) of primary and key secondary variables on selected scenarios

A) All cause death

Scenarios of effect sizes	All cause death Day 180*
All-cause death (HR=0.80); WHF (HR=0.70)	83
All-cause death (HR=0.816); WHF (HR=0.70)	77

All-cause death (HR=0.82); WHF (HR=0.70)	70
All-cause death (HR=0.80); WHF (HR=0.80)	82
All-cause death (HR=0.816); WHF (HR=0.80)	76
All-cause death (HR=0.82); WHF (HR=0.80)	70

Note: The true HR for CV death is assumed to be 0.78 in all scenarios.
*Power if one or both of the two primary variables are significant.

B) CVD, WHF, LOS and CVDR

Scenarios of effect sizes	CV death Day 180	WHF Day 5	LOS	CV death or HF/RF hosp.	Reject All
WHF (HR=0.7) – LOS (0.9 days) – CVD/rehosp (HR=0.85)	82	99	93	93	77
WHF (HR=0.7) – LOS (0.9 days) – CVD/rehosp (HR=0.88)	82	99	92	79	68
WHF (HR=0.7) – LOS (0.7 days) – CVD/rehosp (HR=0.85)	82	99	78	93	69
WHF (HR=0.7) – LOS (0.7 days) – CVD/rehosp (HR=0.88)	82	99	77	77	60
WHF (HR=0.8) – LOS (0.9 days) – CVD/rehosp (HR=0.85)	82	82	87	87	68
WHF (HR=0.8) – LOS (0.9 days) – CVD/rehosp (HR=0.88)	82	82	86	73	59
WHF (HR=0.8) – LOS (0.7 days) – CVD/rehosp (HR=0.85)	82	81	73	86	60
WHF (HR=0.8) – LOS (0.7 days) – CVD/rehosp (HR=0.88)	81	81	72	72	53

Note: The true HR for CV death is assumed to be 0.78 in all scenarios.

Note: The power for the WHF endpoint is approximated based on logrank test, but the analysis will be based on Gehan-Wilcoxon test.

11 Ethical considerations

11.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the 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.

11.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, 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 should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should 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 should 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 child bearing potential should 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.

11.3 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.

11.4 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.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should 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 should 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 CSR.

12.1 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 should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days or less, if required by local regulations.

13 References

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14 Appendix 1: Clinically notable laboratory values

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

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 Section 7.3 Liver safety monitoring
AST (SGOT)	See Section 7.3 Liver safety monitoring
BUN	>100% increase
Creatinine	>100% increase
Total bilirubin	See Section 7.3 Liver safety monitoring
Alkaline phosphatase	>100% increase
Potassium	>25% increase, >25% decrease
Calcium*	>20% increase, >20% decrease
Uric acid*	>100% increase

*Collected in the laboratory substudy only

15 Appendix 2: Liver event and laboratory trigger definitions and follow-up requirements

Table 15-1 Definitions of 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	• 3 x ULN < ALT/AST ≤ 5x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
Liver events	• ALT or AST > 5 x ULN • ALP > 2 x ULN (in the absence of known bone pathology) • TBL > 2 x ULN (in the absence of know Gilbert syndrome) • Potential Hy's Law cases (defined as ALT or AST > 3 x ULN and TBL > 2 x ULN (mainly conjugated fraction) without notable increase in ALP to > 2 x ULN • Any clinical event of jaundice for (or equivalent term) • ALT or AST > 3 x ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting or rash with eosinophilia • Any adverse event potentially indicative of liver toxicity*

* 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

Table 15-2 Follow Up Requirements for liver events and laboratory triggers, 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[a]	Discontinue the study drug immediately Hospitalize, if clinically appropriate Establish causality Complete liver CRF	ALT, AST, fractionated bilirubin[d], Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 x ULN	Discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF	ALT, AST, fractionated bilirubin[d], Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 x ULN	Repeat LFT within 48 hours If elevation persists continue follow-up monitoring If elevation persists for *more than 2 weeks*, discontinue the study drug Establish causality Complete liver CRF	ALT, AST, fractionated bilirubin[d], Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 x ULN accompanied by symptoms[b]	Discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF	ALT, AST, fractionated bilirubin[d], Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 x ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 x ULN In the absence of known bone pathology	Repeat LFT within 48 hours If elevation persists, establish causality Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		

Criteria		Actions required	Follow-up monitoring
> 2 x ULN (in the absence of known Gilbert syndrome		Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF	ALT, AST, fractionated bilirubin[d], Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 x ULN (patient is asymptomatic)		Repeat LFT once or twice in the week. If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Preferred terms			
Jaundice		Discontinue the study drug immediately Hospitalize the patient Establish causality Complete liver CRF	ALT, AST, fractionated bilirubin[d], Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
"Any AE potentially indicative of a liver toxicity*	Medically significant	Consider study drug interruption or discontinuation Hospitalization if clinically appropriate Establish causality Complete liver CRF	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

[a] Elevated ALT/AST > 3 x ULN and TBL > 2 x ULN but without notable increase in ALP to > 2 x ULN

[b] (General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

[c] 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.

[d] Fractionated bilirubin includes testing for total bilirubin, direct bilirubin, and indirect bilirubin.

16 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_2O, is converted into one of 3 categories:

<6 cm H2O	Complete absence of discernable venous wave throughout respiratory cycle above the clavicle, even with hepatic compression (HJR)
6-10 cm H2O	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 H2O). Presence of venous wave only with mild HJR should be graded in this category.
>10 cm H2O	Presence of venous wave throughout respiratory cycle with wave sometimes ≥ 4 cm H2O above clavicle and typically increased with HJR. Patients with values of 6-10 cm H2O 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).