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Clinical Development

RLX030A

Clinical Trial Protocol CRLX030A2302 / NCT02007720

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

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[redacted]

List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AHF	Acute heart failure
Alb	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
b.i.d.	twice a day
BP	Blood pressure
CCU	Coronary care unit
CEC	Clinical Event Committee
CRF	Case Report/Record Form (paper or electronic)
CPO	Country Pharma Organization
CRO	Contract Research Organization
Css	Steady state concentration
CTRD	Clinical Trial Results Database
CV	Cardiovascular
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ER	Emergency Room
ED	Emergency Department
GCP	Good Clinical Practice
HA	Health authority
HF	Heart failure
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form

[redacted]

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IN	Investigator Notification
IV	Intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
IWRS	Interactive Web Response System
JVP	Jugular venous pulse
LFT	Liver function test
LOS	Length of stay
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
PK	Pharmacokinetics
PT	Preferred Term
RF	Renal failure
SAE	Serious adverse event
SBP	Systolic blood pressure
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TD	Study Treatment Discontinuation
ULN	Upper limit of normal
VAS	Visual analog scale
WHF	Worsening heart failure
WoC	Withdrawal of Consent

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
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* protocol-specified concomitant background therapies when these are standard treatments in that indication
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT/IWRS
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
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
Subject/Patient Number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Amendment 4

Amendment rationale

The purpose of this amendment is to implement the following changes as recommended by the study Executive Committee:

1. 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 criterion, the study Executive Committee recommended the following changes:
   - The BNP and NTproBNP inclusion criteria will be increased: BNP ≥500 pg/mL and NT proBNP ≥2000 pg/mL
2. Exclusion criteria for the upper limit of blood pressure at study entry will be added as recommended by the Data Monitoring Committee and endorsed by the study Executive Committee: patients with systolic blood pressure > 180 mmHg at end of screening will be excluded.

Changes to the protocol

- Inclusion criterion #3 has been updated with BNP ≥500 pg/mL and NT proBNP ≥2000 pg/mL
- Exclusion criterion added: Patients with systolic blood pressure > 180 mmHg at the end of screening will be excluded
- Table 6.1 was updated to include:
  - Urine pregnancy test for females at Discharge
  - Assessments of "blood pressure and heart rate" and "body temp and respiratory rate" on Days 60 and 180 to align with section 6.5.2
  - Contact IRT/IWRS at screening
- Section 9.7: To preserve the target study power, the sample size may have to be increased. The Section 9.7 'Sample size calculation' has been updated accordingly.
- Changes have been made to comply with the updated protocol template:
  - Updates/changes to cover page
  - List of abbreviations: additional abbreviations have been added
  - Glossary of terms: additional term has been added
  - Sections 5.4, 5.5. 7.1 7.2, 7.4, and 8.1 have been updated
  - Section 10.3 "Responsibilities of the investigator and IRB/IEC" has been added
  - Section 10.4 "publication of study protocol and results" has been added
  - Section 10.5 "Quality Control and Quality Assurance" has been added
- Other minor clarifications, administrative, and typographical changes have been implemented throughout the protocol.

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.

[redacted]

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

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

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

Summary of previous amendments

Amendment 3

Amendment rationale

The purpose of this amendment is to implement the following changes as requested by the Health Authority in Japan:

1. Add Japanese approved contraceptive methods to the eligibility criterion (exclusion criterion #14). This applies only to patients that are recruited for the trial in Japan.
2. Add the wording to the "History of hypersensitivity to serelaxin or its any ingredients" to the eligibility criterion as it was done in the Japanese local phase II trial CRLX030A1201 (exclusion criterion #16). This applies to any patients that are recruited for the trial in all the participating countries.

Changes to the protocol

- Inclusion criteria #7 has been updated to include the permission for using modified sMDRD formula for eGFR estimation in specific ethnic groups where appropriate.
- There is an overlapping redundancy in the Exclusion criteria #2 and # 9. The two exclusion criteria were combined into a single one.
- Exclusion criterion #10 was removed due to the redundancy, as organ transplant is already included in exclusion criterion #12.
- Exclusion criterion #13 has been updated to include Japanese approved contraceptives as requested by Japanese HA. This is applicable only to patients that are recruited to the study in Japan.
- Exclusion criterion #15 has been clarified to include: serelaxin "or its any ingredients" per comment from the Japanese HA.
- Exclusion criterion #11 was added to comply with the protocol template: 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 years
- Table 6.1: Patient reported dyspnea (LIKERT): assessment at 0 hour was removed as it was inadvertently checked
- Table 6.1: Vital signs assessments were clarified to align with section 6.5.2
- Section 9.4.4 Supportive analyses: the number of sensitivity analyses "two" was removed
- Section 12: Four references have been added

[redacted]

Other minor clarifications, administrative, and typographical changes have been implemented throughout the protocol.

The changes herein do not affect the global Informed Consent. The local ICF in Japan need to be updated to reflect the change made to exclusion criteria #13.

Summary of previous amendments

Amendment 2

Amendment rationale

The purpose of amendment 2 is to implement the following changes:

1. An independent pharmacist or qualified site personnel will prepare the study drug to further enhance the blind in the trial. An independent field monitor model will also be implemented. Further information can be found in the Pharmacy Manual.
2. To ensure consistency in the diagnosis and data collection of the index in-hospital worsening heart failure, the index in-hospital WHF events will be adjudicated by the Clinical Events Committee (CEC).

Changes to the protocol

- The independent pharmacist or qualified site personnel and field monitor model has been incorporated in sections: 5.1.1, 5.4, 5.5.2, 5.5.3, 5.5.4, and 6.3.
- Requirement for CEC to adjudicate index in-hospital worsening heart failure events has been added to sections 6.4.4.2 and 8.5
- Inclusion criterion #3 (first bullet) has been amended to emphasize the dyspnea status at the time of randomization: Persistent dyspnea at rest or with minimal exertion at screening and at the time of randomization
- Exclusion criterion #1 has been clarified as: Description of non-cardiac causes was added: Dyspnea primarily due to non-cardiac causes, such as acute or chronic respiratory disorders or infections (i.e., severe chronic obstructive pulmonary disease, bronchitis, pneumonia), or primary pulmonary hypertension sufficient to cause dyspnea at rest, which may interfere with the ability to interpret the primary cause of dyspnea.
- Exclusion criterion #6: “uncorrected” was added to further clarify the left ventricular outflow obstruction: 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 >50 mmHg on prior or current echocardiogram), and severe mitral stenosis
- Exclusion criterion #14 – has been updated for clarification to include the use of methods of contraception during dosing of study treatment and for 5 days following the cessation of study treatment and to emphasize highly effective contraceptive methods.
- Exclusion criterion #19 was updated to include additional other medical conditions: 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

[redacted]

drug or alcohol abuse or psychiatric disorders, sufficient to interfere with the patient's ability to comply with the protocol instructions or follow-up procedures.

- The following additional objective was added to the "other objectives" and incorporated in sections 2.2, 6.4.2, and 9.4.2 in order to evaluate possible variations in the definition of in-hospital worsening heart failure: time to worsening heart failure through Day 5 where the worsening heart failure is defined by symptoms only, signs only, and by both symptoms and signs
- Table 6-1 Visit assessment – In hospital worsening heart failure assessments at discharge visit was added.
- Section 7 was updated for clarity and according to the updated protocol template
- Section 9.4.2 was amended to clarify the analysis method
- Liver event laboratory requirements have been updated in Appendix 2 Table 14-1 and Table 14-2.

Amendment 1

Short summary of the amendment rationale and changes

The purpose of this amendment is to update the exclusion criteria to be consistent with the amended protocol for the ongoing RELAX-AHF 2 (CRLX030A2301) study as endorsed by the study Executive Committee. The exclusion criterion for the use of inotropes 2 hours prior to screening has been changed to 2 hours prior to randomization to improve recruitment (exclusion criterion #7).

In addition updates to the following sections have been updated to be consistent with the RELAX-AHF 2 amended protocol:

- The definition of worsening heart failure (WHF) has been revised (sections 2.1, 6.4.1, 6.4.4.2, 7.2.2). The time for assessing worsening heart failure "24 hours or more after initiation of study drug" was removed.
- Section 4.1 Inclusion criteria: A footnote related to inclusion criteria #1 was added to clarify assessments that can be used to support patient screening.
- Section 5.5.4 Instructions for prescribing and taking study treatment: A 4 hour window for initiating treatment after randomization was added.
- Table 6-1 Visit assessment – table was updated to reflect the revised WHF definition
  - Worsening heart failure assessments at 6 and 12 hour after initiation of infusion was added

[redacted]

Protocol synopsis

Protocol number	CRLX030A2302
Title	A multicenter, randomized, double-blind, placebo controlled phase III 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 Asian patients with acute heart failure (AHF)
Sponsor and Clinical Phase	Novartis/III
Investigation type	Biologic
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 for 48 hours within 16 hours of clinical presentation, when added to standard therapy, in approximately 1,520 primarily Asian AHF patients randomized to receive serelaxin or placebo to demonstrate superiority in early improvement in signs and symptoms of congestion and reduction in worsening heart failure (WHF) as evaluated by a clinical composite as the primary endpoint. In addition the study will also assess the effect of serelaxin on the cardiovascular (CV) and all-cause deaths as listed as secondary endpoint. The results of which will be interpreted along with the results from other global studies Acute heart failure (AHF) is a major public health problem with high disease prevalence associated with high mortality, morbidity, and financial costs. It is the most common cause of hospitalization in patients 65 years and older (Hunt et al 2009). As its prevalence is projected to increase by 25% over the next 20 years (Heidenreich et al 2011), the burden of HF for health care systems will also increase. Coronary artery disease and hypertension are common causes for AHF in Western countries (Yancy et al 2013, McMurray et al 2012); similar etiology was also found in Asian countries in recent years (Jiang H and Ge J, 2009, Shiba and Sjimokawa 2008, Oh et al 2013, Youn YJ, et al 2012). Similar to the US and Europe, AHF remains an unmet medical need in Asian countries and the leading cause for hospital admissions (Goda et al 2009, Park et al 2010). The study is being conducted primarily in Asian countries for the generation of clinical evidence in AHF patients to fulfill the requirements by the local health authorities in these countries. The trial is designed to demonstrate the clinical benefits in early relief of signs and symptoms of congestion and prevention of worsening heart failure by serelaxin on top of standard care. The study will also collect evidence to evaluate the effect of serelaxin on the reduction of CV mortality in Asian AHF patients.
Primary Objective(s)	To demonstrate that serelaxin is superior to placebo in improving the clinical composite of “treatment success,” “treatment failure” and “ unchanged”

[redacted]

	• Treatment success is defined as moderate or marked improvement in patient reported dyspnea by Likert scale AND at least 2 points improvement for at least 2 out of 4 physician assessed signs and symptoms including orthopnea, rales, edema and jugular venous pulse (JVP) and none of them deteriorating (≥ 0 point improvement) at Day 2. Refer to the efficacy assessment 1 Section 6.4.1 and the physician assessment of signs and symptoms Section 15 Appendix 3. • Treatment failure is defined as in-hospital worsening heart failure or re-hospitalization due to heart failure or renal failure (RF) or death through Day 5. • All remaining patients are classified as having unchanged treatment status if they meet neither the criteria for treatment success at Day 2 nor the criteria for treatment failure through Day 5.
Secondary and other objectives	**Secondary objectives** • To evaluate the effect of serelaxin as compared to placebo on reducing time to in-hospital worsening heart failure through Day 5 • To evaluate the effect of serelaxin as compared to placebo on reducing cardiovascular deaths through a follow up period of 180 days • To evaluate the effect of serelaxin as compared to placebo on reducing all-cause deaths during a follow-up period of 180 days **Other efficacy objectives** • To evaluate the effect of serelaxin as compared to placebo on reducing time to moderate or marked improvements in dyspnea assessed by Likert scale through Day 5 • To evaluate the effect of serelaxin as compared to placebo on changes of dyspnea assessed by VAS-AUC through Day 5 • To evaluate the effect of serelaxin as compared to placebo on reducing the time in index ICU/CCU through Day 5 • To evaluate the effect of serelaxin as compared to placebo in prevention of renal dysfunction or in-hospital worsening of renal function through Day 5 • To evaluate the effect of serelaxin as compared to placebo on reducing the time to re-hospitalization due to HF and renal failure through Day 180 • To evaluate the effect of serelaxin as compared to placebo on reducing the composite endpoint of CV death or re-hospitalization due to HF/renal failure through Day 180 • To evaluate the effect of serelaxin as compared to placebo on time to in-hospital worsening heart failure through Day 5 where the in-hospital worsening heart failure is defined by symptoms only, signs only, and by both symptoms and signs • To evaluate the effect of serelaxin as compared to placebo on reducing the total intravenous loop diuretic dose, vasoactive and inotropes drug usage through Day 5 • To evaluate the effect of serelaxin as compared to placebo on the changes from baseline in cardio-renal biomarkers on Days 2 and 5 **Safety** • To evaluate the safety and tolerability of intravenous serelaxin in AHF

[redacted]

	patients.
Study design	Multicenter, randomized, double-blind, placebo-controlled study
Population	The study population will consist of AHF Asian patients who typically present with normal to elevated BP and decreased renal function and those who meet the inclusion and exclusion criteria.
Inclusion 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 ≥ 30kg and ≤160 kg 3. Hospitalized for AHF; AHF is defined as including all of the following measured at any time between presentation (including the emergency department and outpatient clinic) and the end of screening: • Persistent dyspnea at rest or with minimal exertion at screening and at the time of randomization • Pulmonary congestion on chest radiograph • BNP ≥500 pg/mL or NT-proBNP ≥ 2,000 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 and outpatient clinic 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 7. Impaired renal function defined as an eGFR between presentation and randomization of ≥ 25 and ≤75mL/min/1.73m^2, calculated using the sMDRD formula (or modified sMDRD formula according to specific ethnic groups and local practice guidelines). (Levey et al 2006; Ma et al 2006; Matsuo et al 2009; Townamchai et al 2013) * *Patient assessments of AHF that are per current local institutional/hospital standard protocol or part of routine clinical care that are performed within 16 hours from presentation are allowed before signing informed consent, and can be used to support patient screening.*
Exclusion criteria	1. Dyspnea primarily due to non-cardiac causes such as acute or chronic respiratory disorders or infections (i.e., severe chronic obstructive pulmonary disease, bronchitis, pneumonia), or primary pulmonary hypertension sufficient to cause dyspnea at rest, which may interfere with the ability to interpret the primary cause of dyspnea. 2. Temperature >38.5°C (oral or equivalent), sepsis, active and clinically significant infection requiring IV anti-microbial treatment, or known presence or evidence of Human Immunodeficiency Virus (HIV) infection (based on history and/or clinical findings, including laboratory results obtained during screening period). 3. Clinical evidence of acute coronary syndrome currently or within 30 days prior to enrollment. (Note that the diagnosis of acute coronary syndrome is a clinical diagnosis and that the sole presence of elevated troponin concentrations is not sufficient for a diagnosis of acute coronary syndrome, given that troponin concentrations may be significantly increased in the setting of AHF).

[redacted]

	4. Patients with systolic blood pressure >180 mmHg at the end of screening 5. 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 6. Patients with Hematocrit <25%, or a history of blood transfusion within the 14 days prior to screening, or active life-threatening gastrointestinal (GI) bleeding 7. 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 >50 mmHg on prior or current echocardiogram), and severe mitral stenosis 8. 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 and carperitide), 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 screening. 9. Hepatic disease unrelated to HF etiology and as determined by any one of the following: AST and/or ALT values exceeding 3 X ULN and/or bilirubin > 1.5 X ULN at screening, history of hepatic encephalopathy, esophageal varices, or portacaval shunt, diagnosis of cirrhosis, chronic Hepatitis B or chronic Hepatitis C infection by any means (e.g. based on history, clinical findings, laboratory results or imaging) 10. Major surgery, including implantable devices (e.g. ICD, CRT), or major neurologic event including cerebrovascular events, within 30 days prior to screening 11. Any major solid organ transplant recipient or planned/anticipated organ transplant within 1 year. 12. 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 13. 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 14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study treatment and for 5 days following the cessation of study treatment. 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, symptom thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Refer to Section 4.2 exclusion criteria #13 for complete details. 15. Use of other investigational drugs within 30 days prior to screening 16. History of hypersensitivity to serelaxin or its any ingredients

[redacted]

	17. History of participating in serelaxin clinical studies 18. Inability to follow instructions or comply with follow-up procedures 19. Any other medical conditions that may put the patient at risk or influence study results in the investigator's opinion, or that the investigator deems unsuitable for the study, including drug or alcohol abuse or psychiatric disorders, sufficient to interfere with the patient's ability to comply with the protocol instructions or follow-up procedures
Investigational and reference therapy	• Serelaxin (30 µg/kg/day) administered by body weight category (Table 5-1) infused over 48 hours • Placebo

Efficacy assessments	**Primary efficacy assessment**
	The primary efficacy variable is defined as the clinical composite endpoint based on:
	• Treatment success defined as
	  • Moderate /marked improvement in dyspnea by the Likert Scale at Day 2 AND ≥ 2 points improvement in ≥2 of 4 physician assessed symptoms and signs of congestion (orthopnea, edema, rales and JVP) and none of them deteriorating (≥ 0 point improvement) at Day 2 Refer to the physician assessment of signs and symptoms, Section 15 Appendix 3.
	• Treatment failure defined as
	  • In-hospital worsening heart failure through Day 5 or
	  • All-causes of death through Day 5, or re-hospitalization due to heart failure or renal failure through Day 5
	• Unchanged defined as
	  • All remaining patients are classified as having unchanged treatment status if they meet neither the criteria for treatment success at Day 2 nor the criteria for treatment failure through Day 5.
	If a patient is determined as treatment failure through Day 5, then he/she will be excluded from the assessment of treatment success at Day 2 or unchanged even if the patient experience improved signs and symptoms at Day 2.
	Secondary assessments
	• Time to WHF through Day 5
	• Time to cardiovascular death during a follow-up period of 180 days
	• Time to all-cause death through a follow-up period of 180 days
	Other secondary efficacy assessments:
	• Time to moderate or marked improvements in dyspnea by Likert scale through Day 5
	• Dyspnea by VAS-AUC changes through Day 5
	• Length of stay in index ICU/CCU
	• Renal dysfunction & prevention of in-hospital worsening of renal function through Day 5
	• Time to re-hospitalization due to HF and renal impairment through Day 180
	• Time to CV death or re-hospitalization due to HF/RF through Day 180

[redacted]

	• Time to in-hospital worsening heart failure through Day 5 where the in-hospital worsening heart failure is defined by symptoms only, signs only, and by both symptoms and signs • Use of loop diuretics and vasoactive agents through Day 5 • Changes in cardio-renal biomarkers (Days 2 and 5)
Safety assessments	• Physical examination • Vital signs • Height and weight • Laboratory evaluations • Electrocardiograph
Other assessments	• Healthcare resource utilization (RU parameter) • Pharmacokinetics • Immunogenicity
Data analysis	The primary efficacy variable will be the trichotomous clinical composite endpoint based on (i) treatment 'success' of congestion improvement of dyspnea in Likert (moderately and markedly improvement) AND at least 2 points improvement for at least 2 out of 4 signs and symptoms variables at Day 2, (ii) treatment 'failure' of in-hospital worsening heart failure, death or re-hospitalization due to HF or RF through Day 5 and (iii) neither as 'no change'. The primary analysis will be the comparison of two trinomial distributions of trichotomous clinical composite endpoint between placebo and serelaxin groups. The primary statistical hypothesis is: H_0: $\theta \geq 1$ vs H_a: $\theta < 1$ Where θ is the common value of two odds ratios of clinical composite endpoint ('failure' versus combined 'no change' and 'success' or combined 'failure' and 'no change' versus 'success') between placebo and serelaxin. H_0 is the null hypothesis and H_a is the alternative hypothesis (Whitehead 1993). The hypothesis will be tested based on the FAS with an ordered logistic-regression (proportional odds) model that includes treatment and country as factors (McCullagh, 1980). Given the classification of (-1 denoting 'failure', 0 for 'no change' and 1 for 'success', an odds ratio of less than 1 would favor serelaxin. The odds ratio and 95% confidence interval for the treatment effect will be calculated and presented. There are three secondary variables: • WHF through Day 5 • CV death through Day 180 • All-cause death through Day 180. All of these secondary variables are time-to-event variables. The hypothesis will be tested based on the FAS at a significance level of 0.025 (one-sided). The three secondary variables will be tested using hierarchical testing procedure in controlling overall α of 0.05 (Bretz, et al 2009). If primary endpoint is significant, WHF will be tested first at α of 0.05. If WHF is significant at the same α level then will proceed to test CV death and only

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	if CV death is significant then will test all-cause death at α of 0.05. Time to WHF through Day 5 will be analyzed using Gehan's generalized Wilcoxon test. Patients died in the 5-day period will be considered as having WHF event. Patients without an event will be censored at the earlier of the last contact date or 120 hours after randomization. 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. CV death and all-cause death will be analyzed with a log-rank test. 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. In addition, for CV death and all-cause death, 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. For CV death, a patient without an event will be censored at the earlier of: • Date of death for non-CV related causes • The last date at which the vital status was known • Day 180 For all-cause death, a patient without an event will be censored at the last date at which the vital status was known or at Day 180. **Safety variables** The incidence of adverse events (AEs) recorded through Day 5 and the incidence of serious adverse events (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. AEs with an onset between informed consent and study drug initiation will be listed separately. AEs will be coded using MedDRA. All reported AEs will be summarized by system organ class (SOC) and preferred term by treatment groups. SAEs will be summarized similarly. **Interim analysis** There will be no formal efficacy interim analysis.
Key words	Acute Heart Failure (AHF), Congestion, Worsening Heart Failure (WHF), Renal Impairment, Serelaxin, Biologic.

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1 Introduction

1.1 Background

Acute heart failure (AHF) is a major public health problem with high disease prevalence associated with high mortality, morbidity, and financial costs. It is the most common cause of hospitalization in patients 65 years and older (Hunt et al 2009). As its prevalence is projected to increase by 25% over the next 20 years (Heidenreich et al 2011), the burden of HF for health care systems will also increase. Coronary artery disease and hypertension are common causes for AHF in Western countries (Yancy et al 2013, McMurray et al 2012); similar etiology was also found in Asian countries in recent years (Jiang H and Ge J, 2009, Shiba and Sjimokawa 2008, Oh et al 2013, Youn YJ, et al 2012). Similar to the US and Europe, AHF remains an unmet medical need in Asian countries and the leading cause for hospital admissions (Goda et al 2009, Park et al 2010).

AHF is defined as the rapid onset of, or changes in, signs and symptoms of heart failure (HF) requiring urgent therapy, which usually results in hospitalization (McMurray et al 2012). Recent HF registries consistently show that more than 80% of AHF patients present with dyspnea, 60-80% with renal impairment, and >50-75% with normal to elevated systolic blood pressure (BP) (Adams et al 2005, Gheorghiade et al 2006a, Gheorghiade et al 2006b, Gheorghiade et al 2009). AHF is triggered by a combination of (1) pulmonary, central and peripheral venous congestion and (2) hypoperfusion, both of which induce end organ damage and metabolic abnormalities. The pathophysiology of AHF remains complex, which can include 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).

AHF is a clinical syndrome with heterogeneous underlying pathophysiological changes. Multiple symptoms and signs of hypoperfusion and/or congestion can be presented in different AHF patients with varying severities. Severity and changes in the symptoms and signs of congestion are the basis of the clinical management strategy (Yancy et al 2013, McMurray et al 2012).

The importance of congestion in AHF as an essential target of evaluation and treatment has gained wide recognition (Gheorghiade et al 2006b). One of the most important treatment targets for AHF patients is to relieve symptoms and signs of congestion as early as possible. While multiple signs and symptoms can be presented in AHF patients, dyspnea is one of the most common presenting symptoms of congestion and the most common physician-assessed signs and symptoms of congestion include dyspnea on exertion, orthopnea, rales, edema and elevated jugular venous pressure (JVP) (McMurray et al 2012, Gheorghiade et al 2010, Harinstein et al 2011). The overall status and severity of congestion as assessed by various signs and symptoms such as orthopnea, rales, and JVP, is prognostic of clinical outcomes (Wang et al 2005, Wong et al 2007, Peacock et al 2010, Konstam et al 2011, Kelder et al 2011, Drazner et al 2001, Drazner et al 2008, Ambrosy et al 2013). Furthermore, not all AHF

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patients present with all of the symptoms and signs of AHF. Different types of clinical symptoms and signs can be developed in AHF patients with varying severities. Therefore, it is incomplete to evaluate the disease status of AHF by assessing a single clinical symptom. Therefore, a clinical composite endpoint that comprises multiple signs and symptoms of congestion could reflect more holistically the status of congestion and a more clinically reliable indicator for therapeutic efficacy in clinical trials.

Although symptomatic relief does occur in a subset of 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 contribute to the downward-spiral of disease progression with poor clinical outcomes. The presence of worsening HF symptoms confers a poorer prognosis for AHF patients (Damman et al 2007, Metra et al 2008). With currently available therapy, 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% respectively (Lloyd-Jones et al 2010).

Therefore, the main clinical challenges in AHF management are to achieve optimal and sustained resolution of congestion, to prevent in-hospital worsening of heart failure and renal dysfunction, and most importantly, reduce both short- and intermediate-term mortality. However, current standard of care for AHF offers few options available to the practicing physicians and remains largely unchanged over the last few decades: oxygen in case of hypoxemia, 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 but none of these interventions has 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, Yancy et al 2013, McMurray et al 2012). In terms of standard of care, there are no marked differences among the guidelines established for the treatment of AHF in the US, Europe and Asian countries (JCS 2013, McMurray et al 2012, Yancy et al 2013, Lindenfeld et al 2010, Chinese Society of Cardiology 2011) although there are some variations in drugs approved in different countries, e.g. carperitide in Japan (JCS 2013). Based on guidelines listed above, there is currently no Class 1, Level A guideline recommendations for pharmacological treatments of AHF.

Relaxin (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). Relaxin's activity is initiated by binding to its cognate receptor, relaxin family peptide receptor 1 (RXFP1), which is present in the systemic and renal vasculature as well as in human heart (Hsu et al 2002). Studies show that nitric oxide, endothelin type B receptor, vascular endothelial growth factor (VEGF) and cyclic adenosine monophosphate (cAMP) act as mediators for the vasodilatory as well as anti-fibrotic and anti-inflammatory effects of relaxin (Bani et al 1998, Danielson et al 1999, Dschietzig et al 2003, Du et al 2010). With these pleiotropic effects, relaxin 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.

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Serelaxin is a recombinant protein identical in structure to the naturally occurring H2 relaxin. 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), which determined the optimal dose of 30 µg/kg/day to be used in the phase III pivotal study RELAX-AHF (Teerlink et al 2013).

In the RELAX-AHF study, 1,161 AHF patients were randomized to receive either serelaxin (N=581) or matching placebo (N=580) on the background of standard of care AHF treatment. Serelaxin was administered according to a weight-range adjusted dosing regimen at the nominal dose of 30 µg/kg/day. 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. In addition, serelaxin treatment reduced signs and symptoms of congestion and significantly reduced WHF episodes through Day 5 and the overall length of index hospital stay, associated with arrange of other in-hospital clinical benefits. Importantly, sustained benefits beyond the initial 48 hours of therapy were observed with serelaxin treatment, leading to a clinically and statistically significant 37% reduction in the risk of both CV and all-cause mortality through Day 180 (Teerlink et al 2013). These clinical improvements were associated with significant improvements in biomarkers consistent with reduction in end-organ damage in serelaxin treated patients (Metra et al 2013). With respect to safety, the adverse event profile after study drug exposure was generally comparable between serelaxin and placebo. Although more patients treated with serelaxin had blood pressure decreases, the decrease was manageable; the incidence of hypotension was comparable between serelaxin and placebo groups. Fewer patients in the serelaxin arm had an increase of serum creatinine > 0.5 mg/dL at Day 5 versus placebo (p=0.003). There were also fewer treatment emergent events associated with renal impairment, which may indicate preserved renal function. Overall, the data demonstrated that serelaxin was generally safe and well- tolerated.

A confirmatory phase III study RELAX AHF2 (CRLX030A2301) with randomization to 48 hour intravenous administration of serelaxin or placebo within 16 hours of clinical presentation in AHF patients in geographic regions similar to RELAX-AHF trial is planned to further assess the effect of serelaxin on CV death and other clinical outcomes in addition to safety and tolerability. The primary objective of RELAX AHF2 is to demonstrate that serelaxin is superior to placebo in reducing CV death in AHF patients during a follow-up period of 180 days. Data from this study is intended to replicate the reduction in mortality in AHF patients observed in the RELAX-AHF trial.

In order to evaluate the sensitivity in response to serelaxin, a double-blind, placebo-controlled, parallel-group study (CRLX030A2103) was conducted to evaluate the safety, tolerability, and PK/PD in Japanese and Caucasian healthy volunteers. In this study, a 48 hour intravenous infusion of serelaxin at 10, 30 or 100 µg/kg/day dose rates (based on individual body weight) or placebo was given to Japanese healthy subjects (N=32) and compared to a Caucasian cohort (n=8) also received a 48 hour intravenous infusion of serelaxin at 30 µg/kg/day. Japanese and Caucasian subjects were matched in a pair-wise manner by age, gender and

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weight. Plasma concentrations in Japanese subjects treated intravenously with serelaxin 30 µg/kg/day for 48 hours were similar to those in Caucasian subjects treated in the same manner.

Values of other PK parameters (Tmax, Cmax, T1/2, CL, Vss, and MRT) were also similar in Japanese subjects and Caucasian subjects. In addition, statistically significant dose proportionality was shown for the area under the serum concentration time curve over the entire serelaxin dose rate range (10–100 µg/kg/day) in Japanese subjects demonstrating a linear PK profile. There was also no difference in blood pressure between the two populations. Pharmacodynamic parameters in urine (sodium, potassium, chloride, creatinine, urea, and osmotic pressure) showed no clinically important changes. Overall, there were no apparent differences with regards to safety and tolerability between the Japanese and Caucasian healthy subjects.

The current study is a multinational randomized, double-blind, and placebo-controlled Phase III clinical trial to be conducted primarily in Asian countries for the generation of clinical evidence in AHF patients to fulfill the requirements by the local health authorities in these countries. The trial is designed to demonstrate the clinical benefits in early relief of signs and symptoms of congestion and prevention of in-hospital worsening of heart failure by serelaxin on top of standard of care. The study will also collect evidence to evaluate the effect of serelaxin on the reduction of CV mortality in Asian AHF patients.

1.2 Purpose

The purpose of this study is to evaluate the efficacy, safety and tolerability of intravenous infusion of 30 µg/kg/day serelaxin for 48 hours within 16 hours of clinical presentation, when added to standard therapy, in approximately 1,520 primarily Asian AHF patients randomized to receive serelaxin or placebo to demonstrate superiority in early improvement in signs and symptoms of congestion and reduction in in-hospital worsening heart failure as evaluated by a clinical composite as the primary endpoint. In addition the study will also assess the effect of serelaxin on the cardiovascular and all-cause deaths as listed as secondary endpoint; the results of which will be interpreted along with the results from other global studies.

2 Study objectives

2.1 Primary objective(s)

- To demonstrate that serelaxin is superior to placebo in improving the clinical composite of "treatment success," "treatment failure" and " unchanged"
  - Treatment success is defined as moderate or marked improvement in patient reported dyspnea by Likert scale AND ≥ 2 points improvement for at least 2 out of 4 physician assessed signs and symptoms including orthopnea, rales, edema and JVP and none of them deteriorating (≥ 0 point improvement) at Day 2.

    Refer to the Efficacy assessment 1 Section 6.4.1 and the physician assessment of signs and symptoms Section 15 Appendix 3.
  - Treatment failure is defined as in-hospital worsening of heart failure or re-hospitalization due to HF or RF or death through Day 5.

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- All remaining patients are classified as having unchanged treatment status if they meet neither the criteria for treatment success at Day 2 nor the criteria for treatment failure through Day 5.

Worsening heart failure (WHF) is defined as in-hospital worsening signs and/or symptoms of heart failure that require an intensification of intravenous therapy for heart failure or mechanical ventilator, renal or circulatory support. Such treatment can include the institution or up-titration of IV furosemide, IV nitrates or any other IV medication for heart failure, or institution of mechanical support such as mechanical ventilation, ultrafiltration, hemodialysis, intra-aortic balloon pump or ventricular assist device.

2.2 Secondary and other efficacy objectives

Secondary objectives

- To evaluate the effect of serelaxin as compared to placebo on reducing time to in-hospital worsening heart failure through Day 5
- To evaluate the effect of serelaxin as compared to placebo on reducing cardiovascular deaths through a follow-up period of 180 days
- To evaluate the effect of serelaxin as compared to placebo on reducing all-cause deaths during a follow-up period of 180 days

Other efficacy objectives

- To evaluate the effect of serelaxin as compared to placebo on reducing time to moderate or marked improvements in dyspnea assessed by Likert scale through Day 5
- To evaluate the effect of serelaxin as compared to placebo on changes of dyspnea by VAS-AUC through Day 5
- To evaluate the effect of serelaxin as compared to placebo on reducing the time in index ICU/CCU through Day 5
- To evaluate the effect of serelaxin as compared to placebo on prevention of renal dysfunction or worsening of renal function through Day 5
- To evaluate the effect of serelaxin as compared to placebo on reducing the time to re-hospitalization due to HF and renal failure through Day 180
- To evaluate the effect of serelaxin as compared to placebo on reducing the composite endpoint of CV death or re-hospitalization due to HF/renal failure through Day 180
- To evaluate the effect of serelaxin as compared to placebo on time to in-hospital worsening heart failure through Day 5 where the in-hospital worsening heart failure is defined by symptoms only, signs only, and both symptoms and signs
- To evaluate the effect of serelaxin as compared to placebo on reducing the total intravenous loop diuretic dose, vasoactive and inotropes drug usage through Day 5
- To evaluate the effect of serelaxin as compared to placebo on the changes from baseline in cardio-renal biomarkers on Days 2 and 5

Safety

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

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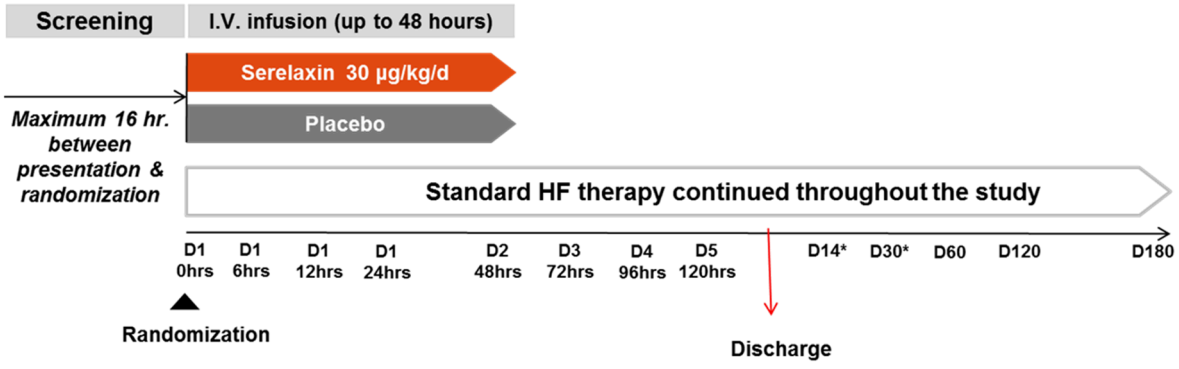
3 Investigational plan

3.1 Study design

Figure 3-1 Study design



* D14 & D30 - Telephone calls

If the discharge visit coincides with a scheduled visit, only the discharge visit will be performed.

Presentation starts as the earliest of (1) time of presentation at either the ER/ED, ICU/CCU, outpatient clinic or ward, (this excludes EMS); 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.

This is a multicenter, randomized, double-blind and placebo-controlled, Phase III clinical trial in primarily multiple Asian countries, designed to evaluate the efficacy and safety of an intravenous infusion of serelaxin when added to standard of care therapy in AHF patients. After assessing eligibility during the screening period, patients who meet the study eligibility criteria will be randomized 1:1 using Interactive Response Technology (IRT)/Interactive Web Response System (IWRS) to receive an intravenous infusion of either serelaxin or placebo in a double-blind manner for up to 48 hours (Figure 3-1). These patients must be randomized within 16 hours of presentation. Presentation starts as the earliest of (1) time of presentation at either the ER, ICU/CCU, outpatient clinic or ward, (this excludes EMS); or (2) time of first IV loop diuretic prior to arrival at the hospital (this includes in outpatient clinic, ambulance, or hospital including emergency department) for the current acute HF episode.

Serelaxin (and/or matching placebo) will be administered as a continuous intravenous infusion for 48 hours according to a weight-range adjusted dosing regimen (see Table 5-1) at the nominal dose of 30 µg/kg/day. Due to the potential risk of hypotension, blood pressure should 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,

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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 recorded 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 up to and including Day 5, and then followed up at scheduled visits for a period of 180 days. 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 on Days 5, 14 (telephone), 30 (telephone), 60, 120 and 180. All AEs will be collected up to and including Day 5 and all serious adverse events (SAEs) will be collected up to and including Day 14, regardless of suspected causality. After Day 14 only suspected SAEs will be collected and reported to Novartis.

3.2 Rationale of study design

This confirmatory Phase III study in Asian AHF patients is designed as a multicenter, randomized, double-blind, and placebo-controlled, study in order to assess the efficacy and safety 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 decision of choosing a clinical composite that is comprising of treatment success, treatment failure and unchanged, as the study primary endpoint is based on complex pathophysiology underlying AHF and the therapeutic goals of AHF treatment. Treatment success at Day 2 targets an early improvement in congestion, and treatment failure through Day 5 aims to prevent clinical worsening of HF, re-hospitalization for HF or RF and death. The clinical composite endpoint of these components is designed to assess the efficacy of serelaxin to the standard care for early and sustainable benefits. It is generally accepted that one of the most important treatment targets for AHF patients is to relieve symptoms and signs of congestion as early as possible (Gheorghiade et al 2006b). While multiple signs and symptoms can be presented in AHF patients, dyspnea is the most common presenting symptom of congestion in AHF patients and the most common physician-assessed signs and symptoms of congestion include dyspnea on exertion, orthopnea, rales, edema and JVP (McMurray et al 2012, Gheorghiade et al 2010, Harinstein et al 2011). It is known that not all AHF patients present with all of the symptoms and signs of congestion. Different types of clinical symptoms and signs can be developed in AHF patients with varying severities.

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Therefore, it is incomplete to evaluate the disease status of AHF by assessing a single clinical symptom. In this study the treatment success at Day 2 is defined by both the moderate or marked improvement in patient reported dyspnea and 2 or more points of improvement in at least 2 out of 4 physician assessed signs of congestion and none of them deteriorating ($\geq$ 0 point improvement). Thus, treatment success requires both relief of patient-reported dyspnea and improvement in physician-assessed signs and symptoms of congestion. This requirement of significant early improvement in multiple signs and symptoms of congestion for treatment success is stringent in recognizing that standard care is generally effective in improving some of the symptoms, e.g. dyspnea. Therefore, a clinical composite endpoint with treatment success as one of the components that is comprised of multiple signs and symptoms of congestion could reflect more holistically the status of congestion and a more clinically reliable indicator for therapeutic efficacy in clinical trials. In summary, the treatment success definition reflects the goals of acute heart failure treatment (ie, relief of dyspnea AND congestion) and represents a comprehensive assessment of the treatment effect.

The clinical composite endpoint has been used as a primary endpoint in several large scale Phase 3 clinical studies in AHF. The major studies include PROTECT study (Massie 2010), REVIVE-2 study (Packer 2013) and the ongoing TRUE-AHF study (Cardiorentis 2013). To assess "treatment success", all the above mentioned 3 studies used a single patient's self-report clinical symptom, such as improvement in dyspnea assessed by Likert scale or improvement in the overall clinical status. The definition of "treatment success" in this RELAX current trial requires both patient-reported improvement in dyspnea assessed by Likert scale and physician-assessed symptoms and signs of congestion (orthopnea, edema, rales and JVP) at Day 2, which is relatively holistic and objective in relation to the clinical status of congestion and reflects the clinical practice adopted worldwide for the treatment of AHF. (JCS 2013, McMurray et al 2012, Yancy et al 2013, Lindenfeld et al 2010, Chinese Society of Cardiology 2011) If a patient is determined as treatment failure, he/she will be excluded from the assessment of treatment success or unchanged even if the patient experienced improved signs and symptoms at Day 2 (i.e., the patient will be considered a treatment failure).

Although there are some variations in the definition of the individual components of the clinical composite, the definition of "treatment failure" in this study, is similar to the one used in the above mentioned 3 studies. The treatment failure in the current study is defined as occurrence of WHF, or death or re-hospitalization due to HF or RF through Day 5. The WHF is defined as 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 furosemide, 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. This definition of WHF is widely accepted (Felker et al 2010, Allen et al 2009) and applied to the above trials.

The primary objective of this study is to demonstrate and confirm the efficacy of serelaxin as compared to placebo to improve the symptoms and signs of congestion at Day 2 and to prevent in-hospital worsening heart failure through Day 5 in Asian AHF patients - an efficacy benefit that was observed in the completed RELAX-AHF study. In addition, CV death and

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all-cause death will be assessed as secondary endpoints in this study; the results of which will be interpreted along with the results from other global studies.

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 and studied in RELAX-AHF study will be evaluated in this phase III confirmatory 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 adjustments and/or discontinuations 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 signs and symptoms of congestion at Day 2, 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 profiles. 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 results of both efficacy and safety were observed in the RELAX-AHF study and the results from the pharmacokinetic (PK) study that showed no evidence of ethnic sensitivity support the adoption of the same weight-based dosing regimen of serelaxin administration in this confirmatory study in Asian AHF patients. The weight category of 30 – 39 kg for dosing is added to accommodate for the possibility of lower body weight in Asian population.

3.4 Rationale for choice of comparator

The current study is designed to demonstrate that serelaxin is superior to placebo on top of standard of care therapy in improving the clinical composite based on improvement in symptoms and signs of congestion and reduction in in-hospital worsening heart failure, re-hospitalization for HF or RF or death as assessed by treatment success, treatment failure and unchanged. There is no evidence based therapy that has been shown to result in both short-term clinical improvements and long- term 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 the entire study period.

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable

3.6 Risks and benefits

Serelaxin infused for 48 hours in both the pre-RELAX-AHF (Teerlink et al 2009) 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 in-hospital worsening heart failure events and length of stay during the index

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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 that 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 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 eligibility 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.

4 Population

The study population will consist of AHF patients who typically present with normal to elevated BP and decreased renal function. The study is aimed to randomize approximately 1,520 patients that meet the eligibility criteria (inclusion criteria Section 4.1, exclusion criteria Section 4.2), primarily, in but not limited to, Asian countries.

4.1 Inclusion criteria

Subjects must fulfill all of the following criteria at screening to be eligible for the study. The screening period is defined as that interval that begins at the time the informed consent is signed and ends with the qualification of the subject for entry into the study (i.e. when subject is determined to meet all eligibility 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 ≥ 30kg and ≤160 kg
3. Hospitalized for AHF; AHF is defined as including all of the following measured at any time between presentation (including the emergency department and outpatient clinic) and the end of screening:
   - Persistent dyspnea at rest or with minimal exertion at screening and at the time of randomization
   - Pulmonary congestion on chest radiograph
   - BNP ≥500 pg/mL or NT-proBNP ≥2,000 pg/mL
4. Systolic BP ≥125 mmHg at the start and at the end of screening

[redacted]

5. Able to be randomized within 16 hours from presentation to the hospital, including the emergency department and outpatient clinic.
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
7. Impaired renal function defined as an eGFR between presentation and randomization of ≥ 25 and ≤75mL/min/1.73m^2, calculated using the sMDRD formula (or modified sMDRD formula according to specific ethnic groups and local practice guidelines). (Levey et al 2006; Ma et al 2006; Matsuo et al 2009; Townamchai et al 2013).

* *Patient assessments of AHF that are per current local institutional/hospital standard protocol or part of routine clinical care that are performed within 16 hours from presentation are allowed before signing informed consent, and can be used to support patient screening.*

4.2 Exclusion criteria

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

1. Dyspnea primarily due to non-cardiac causes, such as acute or chronic respiratory disorders or infections (i.e., severe chronic obstructive pulmonary disease, bronchitis, pneumonia), or primary pulmonary hypertension sufficient to cause dyspnea at rest, which may interfere with the ability to interpret the primary cause of dyspnea.
2. Temperature >38.5° C (oral or equivalent), sepsis, active and clinically significant infection requiring IV anti-microbial treatment or known presence or evidence of Human Immunodeficiency Virus (HIV) infection (based on history and/or clinical findings, including laboratory results obtained during screening period).
3. Clinical evidence of acute coronary syndrome currently or within 30 days prior to enrollment. (Note that the diagnosis of acute coronary syndrome is a clinical diagnosis and that the sole presence of elevated troponin concentrations is not sufficient for a diagnosis of acute coronary syndrome, given that troponin concentrations may be significantly increased in the setting of AHF).
4. Patients with systolic blood pressure >180 mmHg at the end of screening
5. 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
6. Patients with Hematocrit <25%, or a history of blood transfusion within the 14 days prior to screening, or active life-threatening gastrointestinal (GI) bleeding
7. 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 >50 mmHg on prior or current echocardiogram), and severe mitral stenosis
8. Current (within 2 hours prior to randomization) or planned (through the completion of study drug infusion) treatment with any IV vasoactive therapies, including vasodilators

[redacted]

(including nesiritide and carperitide), 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 screening.

9. Hepatic disease unrelated to HF etiology and as determined by any one of the following: AST and/or ALT values exceeding 3 X ULN and/or bilirubin > 1.5 X ULN at screening, history of hepatic encephalopathy, esophageal varices, or portacaval shunt, diagnosis of cirrhosis, chronic Hepatitis B or chronic Hepatitis C infection by any means (e.g. based on history, clinical findings, laboratory results or imaging)
10. Major surgery, including implantable devices (e.g. ICD, CRT), or major neurologic event including cerebrovascular events, within 30 days prior to screening
11. Any major solid organ transplant recipient or planned/anticipated organ transplant within 1 year.
12. 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
13. 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
14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study treatment and for 5 days following the cessation of study treatment. 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, symptom thermal, 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. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
        b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

      For Japan only: Japan approved contraceptive method should be used for patients that are recruited to the study

      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 drug..

[redacted]

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 case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment she is considered not of child bearing potential

15. Use of other investigational drugs within 30 days prior to screening
16. History of hypersensitivity to serelaxin or its any ingredients
17. History of participating in serelaxin clinical studies
18. Inability to follow instructions or comply with follow-up procedures
19. Any other medical conditions that may put the patient at risk or influence study results in the investigator's opinion, or that the investigator deems unsuitable for the study, including drug or alcohol abuse or psychiatric disorders, sufficient to interfere with the patient's ability to comply with the protocol instructions or follow-up procedures

5 Treatment

5.1 Protocol requested treatment

5.1.1 Study and control drugs

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 according to instructions in the *Pharmacy Manual*.

An independent pharmacist or qualified site personnel will prepare the drug for infusion according to the randomization number that is assigned by IRT/IWRS (Section 5.3). In addition an independent study field monitor will be appointed to perform the drug accountability at the sites.

The roles and responsibilities of the pharmacist or qualified site personnel and the field monitor as well as the operational aspect of this model are described in the *Pharmacy Manual.*

5.1.2 Additional treatment

No additional treatment beyond study drug and control drug is included in 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,

[redacted]

ACE inhibitors/angiotensin receptor antagonists, β blockers, and aldosterone receptor antagonists, etc.

5.2 Treatment groups

Subjects will be randomized 1:1 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 IRT to one of the treatment groups. The investigator or his/her delegate will contact the IRT/IWRS after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT/IWRS will assign a randomization number to the patient, which will be used to link the patient to a treatment group 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/IWRS 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 groups, 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/IWRS contacts 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.

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

[redacted]

access to prepare safety and/or efficacy interim analysis reports for the Data Monitoring Committee (DMC). The aforementioned study personnel will not be involved in any other trial activities.

- Study drug will be prepared by an independent pharmacist or qualified site personnel. Drug accountability at the sites will be performed by an independent study field monitor. Although unlikely, the independent pharmacist or qualified site personnel and the field monitor may potentially be unblinded due to the physical presence of the study drug during preparation therefore, the aforementioned study 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 5.5.12), 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. The independent pharmacist or qualified site personnel must not communicate drug information to any other personnel including investigators, study coordinators or other pharmacists at the study site and/or sponsor involved in this trial.
- In the event a patient becomes unblinded for safety reasons during the 48 hour study drug infusion, study drug should be discontinued and the patient should continue study assessments according to protocol.
- The randomization codes associated with patients/subjects from whom PK samples are taken will be disclosed to PK analysts who will keep PK results confidential until data base lock.
- The roles and responsibilities of the pharmacist or qualified site personnel and the field monitor as well as the operational aspect of this model are described in the *Pharmacy Manual.*

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 Patient Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number as given 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/IWRS. The site must select the CRF book with a matching Patient Number from the RDC system to enter data.

If an enrolled patient fails to be treated for any reason, the IRT/IWRS must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the Screening Epoch Study Disposition CRF.

[redacted]

If the patient was correctly randomized in the IRT/IWRS, but treatment was not administered for any reason, the patient must be followed and assessments completed as per Table 6-1 for all the visits until Day 180 All information must be entered into the appropriate eCRFs.

5.5.2 Dispensing the study drug

Each study site will be supplied by Novartis with study drug in packaging of identical appearance. Blinded kits will contain 1 vial of serelaxin or placebo, enough study drug for 24 hours of infusion. Patients with body weight ≥115kg will need 2 vials for a 24h infusion. To receive the second 24 hours of study drug, the investigator's staff will contact the IRT/IWRS again and request a second kit.

The study drug 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 independent pharmacist or qualified site personnel will identify the study drug package(s) to dispense to the patient by contacting the IRT/IWRS and obtaining the medication number(s). Treatment preparation and dispensing should be performed following the procedure, using the material, and within the time laps specified in the Pharmacy Manual (see Section 5.1.1).

The study drug must not be administered to the patient by the person who prepared it.

5.5.3 Handling of study drug

5.5.3.1 Handling of study drug

Study drug 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 independent pharmacist or qualified site personnel and designated assistants have access. Upon receipt, all study drug should be stored in a refrigerator at 2-8°C and protected from light 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.

The independent pharmacist or the qualified site personnel must maintain an accurate record of the shipment, storage and dispensing of study drug in a drug accountability log. Monitoring of drug accountability will be performed by the independent field monitor (who is separate from the monitor who is accountable for the other portions of the study) during site visits and at the completion of the trial.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.12), and at the conclusion of the study. At the conclusion of the study, and as appropriate during the course of the study, the independent pharmacist or the qualified site personnel will return all unused study drug, 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.

[redacted]

5.5.4 Instructions for prescribing and taking study drug

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 as soon as possible but no longer than 4 hours after randomization. Patients need to be randomized WITHIN 16 hours from the time of presentation to hospitals For each randomized patient to receive the study drug according to a weight-range adjusted dosing regimen over a period of 24 hours (Table 5-1), the required amount of study drug will be withdrawn from the 6-ml vials (with 3.5 mL fill) contained in the blinded kits, injected into a 250 mL intravenous bag of 5% dextrose solution, and then infused at a constant rate of 10 mL/hour.

Details of study drug preparation and infusion as well as the roles and responsibilities of the independent pharmacist or qualified site personnel and the field monitor, are described in the Pharmacy *Manual*.

Table 5-1 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
30-39 kg	1.5 mg	1.5 mL
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 dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

5.5.5 Permitted dose adjustments and interruptions of study drug

For patients who experience a systolic BP decrease during the period of study drug infusion, dosing adjustments and/or discontinuations are required and must follow the guidelines described in Table 5-2.

Table 5-2 Dosing adjustment of study drug administration in the event of treatment-emergent 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.

[redacted]

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 hypotension or any safety reasons, re-administration of study drug is not allowed. For non-safety reasons (problems with the infusion line, etc.), dosing may be interrupted once for each patient in general for up to 1 hour in each 24-hour infusion period. If the infusion is stopped for longer than 1 hour, the infusion should still be allowed to continue as long as it is safe for the patient. This time is not to be added back to the end of the infusion and the timed protocol assessments are not to be adjusted. Time from initiation of study drug infusion to completion must not exceed 48 hours. In the event that study drug administration is discontinued for any reason, the patient will continue to be followed at all study visits defined in the protocol.

These changes 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. Use of rescue medication and/or supportive care must be recorded on the appropriate eCRF.

5.5.7 Concomitant treatment

To be eligible for the study, all patients must have received IV furosemide of at least 40 mg (or equivalent) at any time between presentation to emergency services (this includes outpatient clinic, ambulance, or hospital including emergency department) 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 and carperitide), 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. Furosemide may not be administered using the same infusion bag or infusion line as study drug.

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, Days 14 and 30 (telephone visit) and at Days 60, 120 and 180 will be recorded. Only those medications currently being taken or those 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 anti-diabetics, statins, anticoagulants etc.).

[redacted]

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 (#7) with the exception of IV loop diuretics in any patient, or IV nitrates at a dose of ≤ 0.1 mg/kg/hour if the patient has a systolic BP >150 mmHg at screening. Thus, study drug can be started concomitantly with IV nitrates only if at a low dose (≤ 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 eCRF.

5.5.9 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 5-2).
- 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.

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

[redacted]

5.5.10 Withdrawal of informed consent

Patient 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.

In this situation, 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, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessments Table 6-1.

5.5.11 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.5.12 Emergency breaking of assigned treatment code

Emergency treatment code breaks must only be undertaken when it is required in order to treat the patient safely. 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.

Emergency treatment code breaks will be performed using the IRT/IWRS. 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 dependable procedure in place to allow access to the IRT/IWRS at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- patient number

[redacted]

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

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

5.5.13 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.

5.5.14 Early study termination

The study can be terminated at any time for any reason by Novartis. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). 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 / ECs of the early termination of the trial.

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 time point, or as close to it as possible.

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. For all patients it is important that the investigator collects and maintains all available contact information to facilitate the follow-up and to ensure that Day 180 is completed on time.

Patients eligible to participate in this study must be randomized within 16 hours of presentation and treatment should be started as soon as possible but no longer than 4 hours after randomization. Presentation starts at the earliest of (1) time of presentation either at the ER/ED/ICU/CCU, outpatient clinic, or ward (this excludes EMS); 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 that are

[redacted]

performed within 16 hours from presentation 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/IWRS.

[redacted]

Table 6-1 Visit assessment

Epoch	**Screening**		**Randomized Treatment**												
	Screen [d]	**Baseline**	**Study drug infusion[a]**				**Post-treatment daily assessments**					**Follow-up[c]**			
Time points	**Hour -16**	**Hour 0**	**Hour 6**	**Hour 12**	**Hour 24**	**Hour 48**	**Hour 72)**	**Hour 96 (Day**	**Hour 120**	**Discharge[e]**	**Telephone call**	**Telephone call**			**/PSW**
Visits	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**		**109**	**110**	**111**	**112**	**199**
Day		**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5[b]**		**14****	**30****	**60**	**120**	**180**
Visit Date	X	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[n]	X					X			X	X					
Medical History – Protocol Solicited Events	X														
Medical History	X														
Heart Failure and Diabetes History	X														
Alcohol History	X														
Drug Abuse History	X														

[redacted]

Epoch	**Screening**		**Randomized Treatment**												
	Screen [d]	**Baseline**	**Study drug infusion[a]**				**Post-treatment daily assessments**					**Follow-up[c]**			
Time points	**Hour -16**	**Hour 0**	**Hour 6**	**Hour 12**	**Hour 24**	**Hour 48**	**Hour 72)**	**Hour 96 (Day**	**Hour 120**	**Discharge[e]**	**Telephone call**	**Telephone call**			**/PSW**
Visits	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**		**109**	**110**	**111**	**112**	**199**
Day		**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5[b]**		**14****	**30****	**60**	**120**	**180**
Smoking History	X														
Urine Pregnancy Test (CHBP females only) [f]	X									X					X
Body Weight	X				X	X	X	X	X	X			X		X
Height	X														
Physical Examination [h]	S	S			S	S	S	S	S	S			S		S
Blood Pressure and Heart Rate (pulse) measurements [i]	X	X	X	X	X	X	X	X	X	X			X		X
Body Temperature and Respiratory Rate	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					
Patient-reported dyspnea (Likert scale- as ePRO)[s]			X		X	X	X	X	X	X					
Patient-reported dyspnea – VAS scale (as ePRO) [t]		X	X		X	X	X	X	X	X					
Physician assessment of HF signs and symptoms		X	X		X	X	X	X	X	X			X		

[redacted]

Epoch	**Screening**		**Randomized Treatment**												
	Screen [d]	**Baseline**	**Study drug infusion[a]**				**Post-treatment daily assessments**					**Follow-up[c]**			
Time points	**Hour -16**	**Hour 0**	**Hour 6**	**Hour 12**	**Hour 24**	**Hour 48**	**Hour 72)**	**Hour 96 (Day**	**Hour 120**	**Discharge[e]**	**Telephone call**	**Telephone call**			**/PSW**
Visits	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**		**109**	**110**	**111**	**112**	**199**
Day		**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5[b]**		**14****	**30****	**60**	**120**	**180**
In-hospital worsening heart failure assessment[w]			X	X	X	X	X	X	X	X					
Chemistry[j]	X														
Hematology[j]	X														
Laboratory: Central labs– Chemistry[k]		X			X	X	X	X	X	X					
Laboratory: Central labs – Hematology[k]		X			X	X	X	X	X	X					
Blood sample for hepatitis serology[x]		X													
Urine analysis (Dipstick)[l]	S														
Biomarker measurement[u]		X				X			X						
Pharmacokinetic assessment[q]		X				X							X		
Immunogenicity study[r]		X											X		
Concomitant Medications[o]	X	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	X
Assessment of readmission											X	X	X	X	X
Administer study medication		X	→	→	→	→									
Contact IRT/IWRS	X	X			X										
Non serious adverse events[m]		X			X	X	X	X	X	X					

[redacted]

Epoch	**Screening**		**Randomized Treatment**												
	Screen [d]	**Baseline**	**Study drug infusion[a]**				**Post-treatment daily assessments**					**Follow-up[c]**			
Time points	**Hour -16**	**Hour 0**	**Hour 6**	**Hour 12**	**Hour 24**	**Hour 48**	**Hour 72)**	**Hour 96 (Day**	**Hour 120**	**Discharge[e]**	**Telephone call**	**Telephone call**			**/PSW**
Visits	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**		**109**	**110**	**111**	**112**	**199**
Day		**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5[b]**		**14****	**30****	**60**	**120**	**180**
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 in the eCRF; S= assessment to be recorded on source documentation

** Day 14 and Day 30 are telephone visits

[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.

[b] Patients discharged prior to Day 5 will return to the hospital/clinic for Day 5 procedures.

[c] Patients discharged prior to Day 14 will be contacted on Day 14 by telephone for follow-up. The Day 60 and Day 180 assessments will be conducted as outpatient visits if the patient is discharged prior. The Day 30 assessment will be conducted by telephone. 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 and that are performed within 16 hours from presentation 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. Additional samples will be locally-analyzed at Discharge and at the end of study. Refer to Section 6.5.5.

[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 examination will be performed at screening; an abbreviated physical examination will be performed at all other specified time points. Refer to Section 6.5.1

[redacted]

[i] In addition to at screening and baseline, BP and HR (pulse) measurements are to be performed at 30 and 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 up to 48 hours and then every 24 hours until the earlier of Day 5 or Discharge. In addition BP and HR measurements will be taken at Day 60, and Day 180 as part of vital signs assessment. 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 study personnel. The assessments made as per the table above would be entered in the CRFs. Assessments at other time points will be part of source document. Refer to Section 6.5.2

[j] Blood will be locally collected at screening . Refer to Section 6.5.3

[k] Blood will be collected for measurement of biochemistry, hematology and samples shipped to the central laboratory for analysis. Refer to Section 6.5.3.

[m] AEs will be collected from the signing of the ICF to and including Day 5. SAEs will be collected from the signing of the ICF to and including Day 14. After this period, only suspected SAEs will be collected.

[l]Urine dipstick will be measured locally at screening to rule out any conditions requiring further diagnostic evaluation or treatment. Refer to Section 6.5.3.4. .

[n] ECGs will be performed and interpreted locally at screening, at 48 hours, and at Day 5 or discharge, whichever occurs first. The ECG interpretation and person interpreting the ECG must be recorded in the source documents and in the eCRF Refer to Section 6.5.4..

[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 and 30 (telephone visit) and on Days 60, 120 and 180 will be recorded. Only those medications currently being taken or those were taken within 24 hours prior to the visit will be collected.

[p] Withdrawal of consent form is only completed at the time 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

[q]Pharmacokinetics – sample should be taken at 48 hours just prior to end of infusion. If the infusion was discontinued earlier than the complete 48 hour infusion due to whatever the reason, the 48 hour PK serum sample will be collected just prior to the end of infusion if possible and time of collection should be recorded. In addition, PK samples will be collected at baseline and D60 to accompany the immunogenicity samples and support the interpretation of the antibody assay results. Refer to section 6.6.2

[r] Immunogenicity study: blood samples will be collected at baseline and on Day 60 to test the presence of anti-serelaxin antibodies in these study patients. Refer to Section 6.6.3.

[s] Refer to the Dyspnea Measurement by Likert scale Section 16 Appendix 4

[t] Refer to the Dyspnea Measured by Visual Analog Scale (VAS) Section 17 Appendix 5

[u] Biomarkers: blood samples will be taken at baseline, Days 2 and 5. Refer to Section 6.4.4.4

[redacted]

[w] Worsening heart failure is defined as in-hospital 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 furosemide, 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. The investigator will evaluate the patient for in-hospital worsening heart failure events at 6, 12, 24 and 48 hours from the start of study drug infusion, and then daily while hospitalized through Day 5 or at discharge whichever is earlier.

[x] Blood sample will be collected at baseline and stored at the central laboratory for hepatitis serology analysis at a later date as needed in case of a significant liver event. Refer to Section 6.5.3.3

[redacted]

6.1 Information to be collected on screening failures

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

For all patients who have signed informed consent and are entered into the next epoch of the study will have all AEs **occurring after informed consent is signed** recorded on the Adverse Event 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 will be recorded rather than symptoms. 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. Dose Administration Record eCRF will be completed by the site staff including infusions times and rates. Study drug and supplies must be made available for inspection by the independent field monitor for accountability at each visit using vials counts and information provided by the independent pharmacist or the qualified site personnel.

6.4 Efficacy

6.4.1 Efficacy assessment 1

The primary efficacy variable is defined as the clinical composite endpoint based on:

- Treatment success defined as
  - Moderate /marked improvement in dyspnea by the Likert Scale at Day 2 AND ≥ 2 points improvement in ≥2 of 4 physician assessed symptoms and signs of congestion (orthopnea, edema, rales and JVP) and none of them deteriorating (≥ 0 point improvement) at Day 2

    Refer to the physician assessment of signs and symptoms, Section 15 Appendix 3.
- Treatment failure defined as
  - In-hospital worsening heart failure through Day 5 or

[redacted]

  - All causes of death through Day 5, or re-hospitalization due to heart failure or renal failure though Day 5
- Unchanged defined as
  - All remaining patients are classified as having unchanged treatment status if they meet neither the criteria for treatment success at Day 2 nor the criteria for treatment failure through Day 5.

If a patient is determined as treatment failure through Day 5, then he/she will be excluded from the assessment of treatment success or unchanged even if the patient experience improved signs and symptoms at Day 2.

Worsening heart failure (WHF) is defined as in-hospital 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 furosemide, 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.

6.4.2 Efficacy assessment 2

Secondary endpoints will comprise:

- Time to WHF through Day 5
- Time to cardiovascular death during a follow-up period of 180 days
- Time to all-cause death through a follow-up period of 180 days

Other efficacy endpoints will comprise:

- Time to moderate or marked improvements in dyspnea by Likert scale through Day 5
- Dyspnea by VAS-AUC changes through Day 5
- Length of stay in index ICU/CCU
- Renal dysfunction & prevention of worsening of renal function through Day 5
- Time to re-hospitalization due to HF and renal impairment through Day 180
- Time to CV death or re-hospitalization due to HF/RF through Day 180
- Time to in-hospital worsening heart failure through Day 5 where the in-hospital worsening heart failure is defined by symptoms only, signs only, and by both symptoms and signs
- Use of loop diuretics and vasoactive agents through Day 5
- Changes in cardio-renal biomarkers (Days 2 and 5)

6.4.3 Appropriateness of efficacy assessments

The primary efficacy endpoint is defined as the clinical composite comprised of treatment success at Day 2 or treatment failure or unchanged through Day 5. Treatment success is assessed by moderate/ marked improvement in dyspnea measured by Likert Scale at Day 2 AND a minimum of 2 points improvement in at least 2 out of 4 physician assessed symptoms and signs of congestion (orthopnea, edema, rales and JVP) and none of them deteriorating ($\geq$0 point improvement) at Day 2 as compared to baseline. The treatment failure is defined as in-hospital WHF, death, or re-hospitalization through Day 5. To define the treatment success by

[redacted]

improvement in signs and symptoms at Day 2 is to evaluate the early therapeutic effect of serelaxin for the relief of congestion; to define the treatment failure as WHF, death and re-hospitalization through Day 5 is to assess the therapeutic effect is sustained by preventing these in-hospital worsening HF events. If a patient is determined as treatment failure, he/she will be excluded from the assessment of treatment success or unchanged even if the patient experienced improved signs and symptoms at Day 2.

By applying this clinical composite endpoint definition to the data of the completed RELAX-AHF study, the post-hoc analysis showed that the patients who met the definition of "treatment failure" comprised 11.9% in placebo group and 6.4% in the serelaxin group, and the relative risk reduction (RRR) in favor of serelaxin was 45%. The patients who met the definition of "treatment success" comprised 26.0% in placebo group and 31.7% in the serelaxin group (the relative increase in the proportion of "treatment success" was 22%). Using the analysis of maximum likelihood estimates, the serelaxin treatment showed statistically significant benefits in the clinical composite endpoint compared to placebo ($p < 0.001$).

6.4.4 Other efficacy assessments

6.4.4.1 Assessment of AHF signs and symptoms

The investigator will evaluate the signs and symptoms of heart failure, including patient's dyspnea on exertion or at rest, orthopnea, rales, JVP, peripheral edema, and the patient's assessment of dyspnea (Refer to Section 15 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 Day 60. These evaluations should be done at 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. Only physicians who have completed the training of the protocol based standardized measurements can obtain the physician assessed signs and symptoms for this study.

6.4.4.2 Worsening of heart failure

Worsening heart failure (WHF) is defined as in-hospital 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 furosemide, 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.

The investigator will evaluate the patient for early in-hospital worsening heart failure events at 6, 12, 24 and 48 hours from the start of study drug infusion, and then daily while hospitalized through Day 5 or at discharge whichever is earlier (Refer to Table 6-1). These evaluations should be done at 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

[redacted]

together with the first assessor at least once prior to performing the assessments independently. Only physicians who have completed the training of the protocol based standardized measurements can obtain the physician assessed signs and symptoms for this study.

Index in-hospital worsening heart failure events will be adjudicated by the CEC. The procedures of the adjudication will be described in the *CEC Charter*.

6.4.4.3 Re-hospitalization

Re-hospitalization 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.

6.4.4.4 Biomarkers

Biomarkers related to cardiac and renal function/injury will be obtained from blood. Biomarkers sample will be collected at baseline, 48 hours and at Day 5 post infusion.

These analyses will be used to elucidate the effect of serelaxin and to explore drug effect versus baseline biomarkers of risk. Biomarkers such as but not limited to NTproBNP, high sensitivity troponin T, and Cystatin C. This list may be changed or expanded further as it is recognized that more relevant or novel biomarkers may be discovered. Biomarker analysis may be performed during the process of this study or after its completion as new, more relevant biomarkers are identified. Specific handling of the biomarker samples will be described in detail in the Laboratory Instruction Manual.

6.5 Safety

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

6.5.1 Physical examination

An overall physical examination will be performed by the investigational staff at screening and 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.

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 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 SAE must be recorded on the Serious Adverse Event section of the eCRF (Section 7.2), and a

[redacted]

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.

Subjects discharged post study drug infusion (48 hours) but prior to Day 5 will be required to return for a physical examination as an outpatient at Days 5.

6.5.2 Vital signs

Body temperature and respiration rate will be measured at Screening, Baseline, at 24 and 48 hours after start of study drug infusion and daily until Day 5 or discharge and on Days 60 and 180, Patients discharged prior to Day 5 will return to the hospital/clinic for Day 5 procedures.

BP and heart rate (pulse) measurements will be performed at Screening, throughout study drug infusion at 30 and 60 minutes, then every hour for the first 6 hours, and then every 3 hours, including night time hours. Post-infusion, BP and HR are to be measured every 3 hours until 12 hours following end of infusion, then every 6 hours for up to 48 hours and then every 24 hours until the earlier on Day 5 or discharge and at Days 60 and 180. BP and HR are preferred to be measured with the patient in the same position and with the same equipment using the same arm throughout study drug infusion. If different instruments are used, then calibration of these instruments is required and logs are documented by the site and verified by the monitor. These measurements may be made and recorded by trained healthcare personnel as part of their routine clinical duties, as well as study personnel. If at any time during dosing, the subject's systolic blood pressure is decreased by > 40 mm Hg from baseline but is ≥ 100 mmHg in 2 consecutive measurements 15 min apart, serelaxin infusion rate will be decreased by 50% for the remainder of the 48 hour study drug administration. Serelaxin administration will be permanently discontinued at any time if in 2 consecutive measurements; 15 minutes apart, systolic blood pressure is reduced to < 100 mmHg (also see details in Section 5.5.5).

Should the study drug dose be decreased or the study drug be discontinued prematurely due to blood pressure decrease, measurements should be taken every half hour through 2 hours following the blood pressure decrease event, and then hourly through 5 hours after event onset. Upon completion of the 5 hour post event onset time point, heart rate and blood pressure measurements should be resumed as outlined above.

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 and Days 1-5, Discharge, Day 60 and 180. 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.

[redacted]

6.5.3 Laboratory evaluations

A local laboratory will be used for analysis of all specimens collected at screening according to Table 6-1. The laboratory name and value must be entered into the eCRF page. Fasting for the blood collection samples is optional.

A central laboratory will be used for the analysis of all baseline and post-baseline specimens collected according to Table 6-1. All central laboratory results will be communicated by the central lab to the investigators and the sponsor. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual.

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.

6.5.3.1 Hematology

The following hematology tests will be measured locally at screening and centrally at baseline and post-baseline: RBC, hemoglobin, hematocrit, platelet, and white blood cell count, including differentials.

6.5.3.2 Clinical chemistry

The following serum chemistry tests will be measured locally at screening and centrally at baseline and post-baseline: sodium, potassium, glucose, blood urea nitrogen (BUN) or urea, AST, ALT, alkaline phosphatase, total bilirubin, calcium, uric acid and creatinine. In addition, BNP/NT pro-BNP, eGFR and hemoglobinA1c will be measured locally at screening only.

6.5.3.3 Blood sample for hepatitis serology

A blood sample will be collected at baseline and stored at the central laboratory for hepatitis serology analysis in case of a significant liver event.

6.5.3.4 Urinalysis

The following tests are included in the dipstick urinalysis: blood, glucose, ketones, leukocytes, pH, and protein will be measured locally at screening.

6.5.4 Electrocardiogram (ECG)

Triplicate 12 lead ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling.

[redacted]

Triplicate 12 lead ECGs are collected at 48 hours and at Day 5 or discharge, whichever occurs first. The original ECGs on non-heat-sensitive paper / and a certified copy on non-heat sensitive paper, appropriately signed, should be collected and archived at the study site. ECG findings will be recorded in the source documents and on the eCRF.

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

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

6.5.5 Pregnancy and assessments of fertility

At screening, a locally-analyzed urine pregnancy test will be performed for all females of childbearing potential. A positive urine pregnancy test should be confirmed with a serum pregnancy test. Urine pregnancy test will be repeated at Discharge and the end of the study. Any subject with positive confirmed serum pregnancy test at Screening will be excluded from participating in the study.

6.5.6 Appropriateness of safety measurements

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

6.6 Other assessments

6.6.1 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.

6.6.2 Pharmacokinetics

Blood sample collection and processing

[redacted]

Blood samples for PK will be taken at baseline, 48 hr and Day 60. The 48 hr PK sample should be taken prior to the end of infusion. If the infusion was discontinued earlier than the complete 48 hr infusion due to whatever the reason, the 48 hr PK serum sample will be collected just prior to the end of infusion if possible and time of collection should be recorded. The PK samples at baseline and Day 60 are collected as a part of immunogenicity analysis package.

Blood sample will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein contra-lateral to the site of the infusion. If an indwelling cannula is used, a 0.5 mL discard will be taken before he PK sample in case the indwelling cannula was flushed with saline. Serum separator tubes will be used to collect serum for the determination of serelaxin concentrations

For pharmacokinetic analysis of serelaxin, approximately 2 mL blood will be drawn into a serum separator tube. Instructions regarding the sample collection and handling including clotting time, centrifuge temperature and duration, storage and shipment are described in the Laboratory Manual.

All samples will be given a unique sample number (as listed in Appendix 6). The first aliquots should be sent to the bioanalytical center on dry ice, while the back-up aliquots should be sent to the same address after assurance that the first aliquots arrived in good condition. For detailed instructions on labeling and shipment of samples, please refer to the Laboratory Manual.

Pharmacokinetic bioanalytical method

Serelaxin will be determined in serum by a validated Enzyme Linked Immuno Sorbent Assay (ELISA) [redacted]

The detailed method descriptions of the PK assay will be included in the corresponding bioanalytical report.

6.6.3 Immunogenicity

Immunogenicity blood collection and processing

Blood samples for immunogenicity will be taken at baseline and on Day 60. They will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein contra-lateral to the site of infusion. If an indwelling cannula is used, a 0.5 mL discard will be taken before the immunogenicity sample in case the indwelling cannula was flushed with saline. Serum separator tubes will be used to collect serum for the evaluation of anti-serelaxin antibodies.

For assessment of immunogenicity (anti-serelaxin antibody), approximately 3 mL blood will be drawn into a serum separator tube. Instructions regarding the sample collection and handling including clotting time, centrifuge temperature and duration, storage and shipment are described in the Laboratory Manual.

[redacted]

All samples will be given a unique sample number (as listed in Appendix 6). The first aliquots should be sent to the bioanalytical center on dry ice, while the back-up aliquots should be sent to the same address after assurance that the first aliquots arrived in good condition and whenever possible together with the next shipment of first aliquots. For detailed instructions on labeling and shipment of samples, please refer to the Laboratory Manual.

Immunogenicity analytical methods

Anti-serelaxin antibodies will be evaluated in serum in a validated four-tiered assay approach.

All samples are initially screened for potential immunogenicity in the screening assay. Any positive screen results are confirmed using an immunodepletion assay. If a sample immunodepletes, it is considered confirmed positive and the sample moves to a third tier titration assay. Confirmed positive samples will also be tested for neutralization of serelaxin biological activity using a validated bioassay. The detailed method descriptions of the immunogenicity assays will be included in the corresponding bioanalytical data reports.

6.6.4 Pharmacogenetics/pharmacogenomics

Pharmacogenetics will not be performed in this study.

7 Safety monitoring

All AEs will be collected up to and including Day 5, and all SAEs will be collected up to and including Day 14, regardless of suspected causality. After Day 14 only suspected SAEs will be collected and databased.

7.1 Adverse events

An AE is any untoward medical occurrence (e.g, 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 until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

In this study, non-serious AEs will be collected through Day 5, SAEs will be collected through Day 14.

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

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

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

[redacted]

- they require therapy.

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

AEs with an onset up to and including Day 5 must 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 (yes/no)
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported
- whether it constitutes a SAE (See Section 7.2 for definition of SAE) and which seriousness criteria have been met
- action taken regarding study treatment

All AEs 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 treatment permanently discontinued due to this AE
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

The investigator must also instruct each patient to report any new AE (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information 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.

[redacted]

7.2 Serious adverse events

7.2.1 Definition of serious adverse event

A SAE is defined as any AE [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 (specify what this includes)
  - 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, e.g., defined as an event that jeopardizes the patient or may require medical or surgical intervention.

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

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (please refer to Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

7.2.2 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.

[redacted]

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The Investigator must assess the relationship of each SAE to each specific component of the study treatment (if the study treatment consists of several components) complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis.Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an IN to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

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. 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, worsening heart failure, re-hospitalization due to HF, and re-hospitalization due to renal failure.

Note: Worsening heart failure is defined as in-hospital 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 furosemide, IV nitrates or any other IV medication for

[redacted]

heart failure, or institution of mechanical support such as mechanical ventilation, ultrafiltration, hemodialysis, intra-aortic balloon pump or ventricular assist device.

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,

[redacted]

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.

7.3 Liver safety monitoring

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.

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

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

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

Every liver laboratory trigger or liver event as defined in Table 14-1 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 14-2 in Appendix 2.

For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation.

These LFT repeats should be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory should then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the Liver eCRF pages.

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

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate

[redacted]

- 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.

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.

7.4 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent 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 must be recorded on the Pharmacovigilance 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 and unrelated to the pregnancy must be reported on a SAE Form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)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. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

[redacted]

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.

8.2 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.

8.3 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.

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/IWRS 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.

[redacted]

8.4 Data Monitoring Committee

An external independent Data Monitoring Committee (DMC) will be appointed to monitor the safety of study participants and to ensure that the program is being conducted with highest scientific and ethical standards. This DMC will review the AE 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 safety of the patients, this will be communicated by Novartis to HAs, ECs and investigators within an appropriate timeframe.

Details regarding the DMC process will be available in relevant DMC charter.

8.5 Adjudication Committee

An external and independent CEC will review and adjudicate index in-hospital WHF, CV deaths and re-hospitalizations. 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 index in-hospital WHF, re-hospitalization 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.

9 Data analysis

9.1 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 AEs also constitutes a safety assessment. Patients will be analyzed according to treatment received. Patients who received 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
- **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).

* 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/IWRS contacts 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.

[redacted]

9.2 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 by 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.

[redacted]

9.3 Treatments

Overall study drug administration details will be summarized for the RAN population. This will include time from presentation to randomization (hours), time from randomization to study drug administration (hours), 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, PT, and treatment group for the randomized population.

9.4 Analysis of the primary variable(s)

The primary analysis and the analyses of all secondary and other efficacy endpoints will be based on the Full Analysis Set (FAS), following the intention-to-treat principle.

9.4.1 Variable(s)

The primary efficacy variable will be the trichotomous clinical composite endpoint based on (i) treatment ‘success’ of congestion improvement of dyspnea in Likert (moderately and markedly improvement) and at least 2 points improvement for at least 2 out of 4 signs and symptoms variables at Day 2, (ii) treatment ‘failure’ of in-hospital worsening heart failure, death or re-hospitalization due to HF or RF through Day 5 and (iii) neither as ‘no change’.

[redacted]

[redacted]

9.4.3 Handling of missing values/censoring/discontinuations

The components of trichotomous clinical composite endpoint are all categorical variables. Missing categorical value will be replaced with the last preceding non-missing value. These will include dyspnea Likert scale at Day 2, four signs and symptoms at Day 2 and in-hospital worsening heart failure through Day 5. In the evaluation of treatment success for the four signs and symptoms, the change from baseline will need to be calculated. If there is a missing baseline value, say a patient with missing JVP at baseline, this patient's change of JVP at Day 2 will be set as 0-point improvement, i.e., will not be contributed as 2-point improvement for JVP.

[redacted]

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

There are three secondary variables:

- WHF through Day 5
- CV death through Day 180
- All-cause death through Day 180.

All of these secondary variables are time-to-event variables. The hypothesis will be tested based on the FAS at a significance level of 0.025 (one-sided).

The three secondary variables will be tested using hierarchical testing procedure in controlling overall α of 0.05 (Bretz, et al 2009). If primary endpoint is significant, WHF will be tested first at α of 0.05. If WHF is significant at the same α level then will proceed to test CV death and only if CV death is significant then will test all-cause death at α of 0.05.

Time to WHF through Day 5 will be analyzed using Gehan's generalized Wilcoxon test. Patients died in the 5-day period will be considered as having WHF event. Patients without an event will be censored at the earlier of the last contact date or 120 hours after randomization. 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.

For CV death and all-cause death will be analyzed with a log-rank test. 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

[redacted]

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.

In addition, for CV death and all-cause death, 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.

For CV death, a patient without an event will be censored at the earlier of:

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

For all-cause death, a patient without an event will be censored at the last date at which the vital status was known or at Day 180.

[redacted]

Other efficacy variables

Other efficacy variables will comprise:

1. Time to moderate or marked improvements in dyspnea by Likert scale through Day 5
2. Dyspnea by VAS-AUC changes through Day 5
3. Length of stay in index ICU/CCU
4. Renal dysfunction & prevention of in-hospital worsening of renal function through Day 5
5. Time to re-hospitalization due to HF and renal failure through Day 180
6. Time to CV death or re-hospitalization due to HF/RF through Day 180
7. Time to in-hospital worsening heart failure through Day 5 where the in-hospital worsening heart failure is defined by symptoms only, signs only, and by both symptoms and signs
8. Use of loop diuretics and vasoactive agents through Day 5
9. Changes in cardio-renal biomarkers (Days 2 and 5)

Time to moderate or marked improvements in dyspnea by Likert scale through Day 5 (variable number 1) will be analyzed by Wilcoxon rank-sum test. Other time to event variables (5, 6 and 7) will be analyzed by presenting Kaplan-Meier estimates and testing with the log rank test. Change from baseline variables (2) will be analyzed using ANCOVA model with baseline VAS as a covariate. Variables representing the number of days or multi-categorical variables (3) will be analyzed using the Wilcoxon rank-sum test. The categorical variables (4 and 8) will be analyzed using chi-squared tests.

Detailed biomarker analyses (9) (changes in cardio-renal biomarkers at Days 2 and 5) will be included in the Statistical Analysis Plan.

[redacted]

9.5.2 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 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 up to and including Day 5, or from Day 6 up to and including Day 14. After Day 14 only suspected serious adverse events will be collected and reported to Novartis. 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, 1^{st} and 3^{rd} 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.

[redacted]

9.5.3 Resource utilization

Summary statistics on hospital length of stay in index ICU/CCU for the initial and subsequent hospitalizations, as well as procedures rendered during these hospitalizations will be provided by treatment group. Additional information will be provided in the Statistical Analysis Plan.

9.5.4 Health-related Quality of Life

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

9.5.5 Pharmacokinetics

Steady state concentration (Css) will be estimated based on the serum concentration determined at the 48 hr time point prior to the end of infusion. Systemic clearance will be calculated using the rate of infusion and Css for each patient as indicated below:

Clearance (mL/hr/kg) = Rate of infusion (μg/kg/hr) /Css (μg/mL).

Since only sparse PK time points for serelaxin serum concentration will be collected, no other PK parameters will be determined in this study.

Concentrations below the assay LLOQ (BLQ) will be treated as zero for PK parameter calculations.

Descriptive statistics for serelaxin concentrations will be listed by time points (for baseline and 48hr samples only) to include arithmetic mean, geometric mean with its corresponding 90% confidence interval, median, SD, CV, min and max. A value of "0" will be used for samples that are BLQ in these calculations and therefore be excluded from geometric mean calculations. Descriptive statistics include arithmetic mean, geometric mean with its corresponding 90% confidence interval, median, SD, CV, min and max will also be provided for the two PK parameters, Css and clearance.

Subgroup analysis on Css and CL to assess the potential effects of various extrinsic and intrinsic factors on the PK of serelaxin may be performed as appropriate. These factors may include but not limited to age, gender, race, country of origin, concomitant medications, etc. Details of these analyses will be described in the Statistical Analysis Plan.

Serelaxin serum concentration will be assayed in Day 60 samples as well, in order to demonstrate the lack of drug interference with the immunogenicity assay, but this data will be included only as part of the immunogenicity results but not in the PK results.

9.5.6 Immunogenicity

Anti-serelaxin antibodies will be measured in serum samples collected at the Day 60 time point. To account for individual variability in background of each subject and to check for endogenous interference and/or pre-existing anti-serelaxin antibodies, anti-serelaxin antibodies will also be measured at baseline. Frequencies and percentages will be computed for occurrence of anti-RLX030 antibodies at each time point. Listings for subjects with a

[redacted]

positive screening result at any time point will include subject number, time point, immunodepletion result, titer, and neutralizing antibody result.

9.5.7 Pharmacogenetics/pharmacogenomics

Not applicable

9.5.8 Biomarkers

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.

9.5.9 PK/PD

Not applicable

9.6 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.

There will be no formal efficacy interim analysis.

9.7 Sample size calculation

A sample size of 1,520 AHF patients will need to be randomized 1:1 to serelaxin and placebo. This study will have 80% power at a two-sided type-I error of 5% to detect a distributional shift with a common odds ratio of 0.75 between the distributions of placebo and serelaxin [redacted]

The sample size re-estimation is anticipated to be conducted when about 70% of patients have enrolled and the event rates will be calculated based on patients who have data at least through Day 5. If the pooled observed event rates of treatment failure and treatment success

[redacted]

(assessed on a blinded basis) are much lower than expected based on RELAX-AHF data, sample size may be increased to preserve the target study power.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed 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.

10.2 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 must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must 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 (e.g.. all of the procedures described in the protocol). The process of obtaining informed consent must 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 must 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 must not be entered in the study.

10.3 Responsibility of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients/subjects. 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 Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as

required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

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.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance (CQA), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an 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 and health authorities, where required, it cannot be implemented.

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. 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, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

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13 Appendix 1: Clinically notable laboratory values and vital signs

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

Hematology	
RBC count	>50% increase, >25% decrease
Hemoglobin	>50% increase, >25% decrease
Hematocrit	>50% increase, >25% decrease
WBC count	>100% increase, >50% decrease
Platelet count	>100% increase, >50% decrease
Blood Chemistry	
ALT (SGPT)	See Section 7.3 Liver Guidance
AST (SGOT)	See Section 7.3 Liver Guidance
BUN	>100% increase
Creatinine	>100% increase
Total bilirubin	See Section 7.3 Liver Guidance
Alkaline phosphatase	See Section 7.3 Liver Guidance
Potassium	>25% increase, >25% decrease
Calcium	>20% increase, >20% decrease
Uric acid	>100% increase

[redacted]

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

Table 14-1 Liver event and laboratory trigger definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST≤5 x ULN • 1.5 x ULN <TBL≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP >2 × ULN (in the absence of known bone pathology) • TBL >2 × ULN (in the absence of known Gilbert syndrome) • Potential Hy's Law cases (defined as ALT or AST>3 × ULN and TBL >2 × ULN [mainly conjugated fraction] without notable increase in ALP to >2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST >3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity *

Table 14-2 Follow up requirements for liver events and laboratory triggers

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 × 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 × 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 × 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 × 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 × 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)		
> 2 × 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 × 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 or at next visit

[redacted]

Criteria	Actions required	Follow-up monitoring
Preferred Term		
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*	• 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 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × 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

[redacted]

15 Appendix 3: Physician assessment of signs and symptoms

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

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

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

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

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

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

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

[redacted]

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 -15 cm H2O	Presence of venous wave throughout respiratory cycle with wave sometimes ≥ 4 cm H2O above clavicle and typically increased with hepatojugular reflux *(*HJR). Patients with values of >10 cm H2O and positive HJR should be graded in this category.
>15 cm H2O	Same as above with different cut-off value in cm H_2O
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.

[redacted]

16 Appendix 4: Dyspnea Measurement by Likert Scale

Patient will be presented with the following question: "We would like to measure how you think your breathing is. Please circle the number next to the description that best indicates how you are breathing right now, compared to the time just prior to you first started the study drug."

- 3 = Markedly better
- 2 = Moderately better
- 1 = Minimally better
- 0 = No change
- -1 = Minimally worse
- -2 = Moderately worse
- -3 = Markedly worse

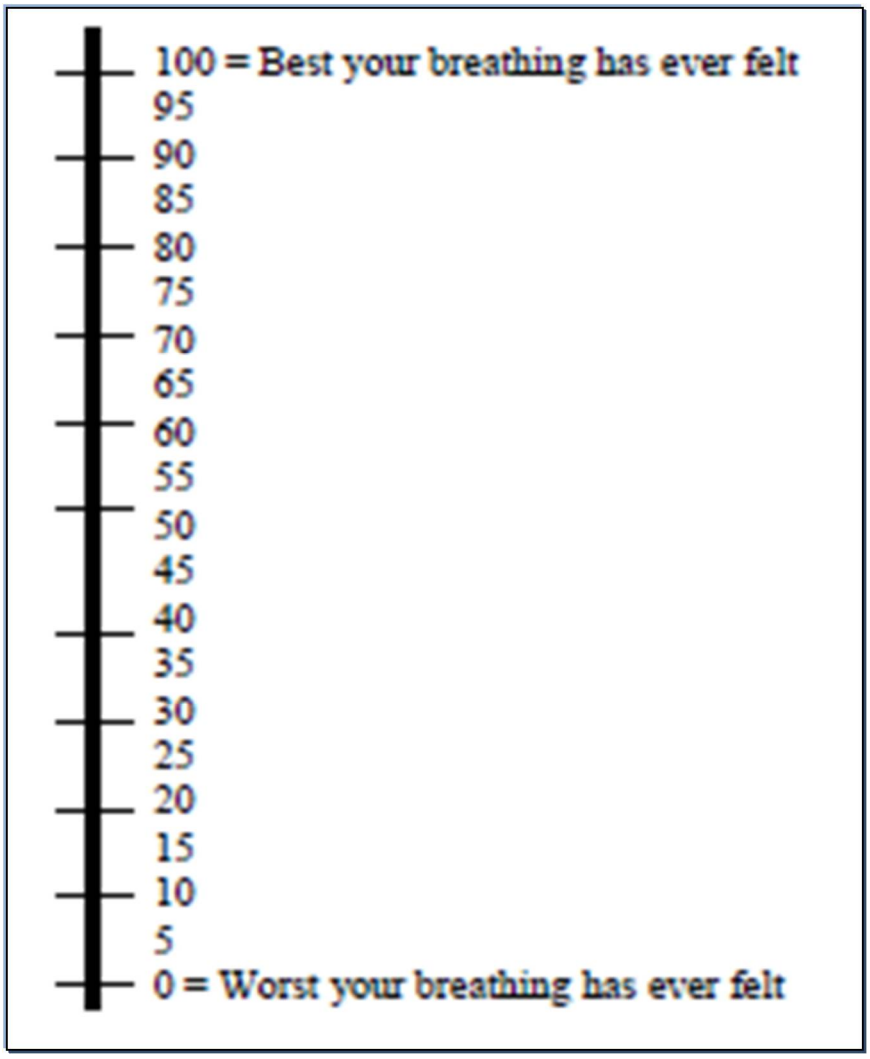
Guidelines:

- All assessments will be done with patient lying in bed; the head of bed should be at 30º, oxygen off for 3-5 minutes before starting assessment.
- If oxygen off is not tolerated, put oxygen back on the patient and assess immediately, asking the patient to describe how he or she felt when the oxygen was off.

[redacted]

17 Appendix 5: Dyspnea Measured by Visual Analog Scale (VAS)

Visual analog scale (VAS): Patient will be presented with the following question: "Please draw a horizontal line on the scale to show how you think your breathing is right now. The number "0" equals the worst your breathing has ever felt and the number "100" equals the best you have ever felt."



Guidelines:

- All assessments will be done with patient lying in bed; the head of bed should be at 30º, oxygen off for 3-5 minutes before starting assessment.
- If oxygen off is not tolerated, put oxygen back on the patient and assess immediately, asking the patient to describe how he or she felt when the oxygen was off.

[redacted]

18 Appendix 6: Blood collection log for PK and immunogenicity samples

Study Phase	Visit No.	Study Day	Time post start of infusion (hr)	PK			IG		Total Volume
				Sample Size (mL)	Sample No.	Dose Ref. ID	Size (mL)	Sample No.	mL per visit
Baseline	101	D1	0 (Pre)	2	101	1	3	201	5
Treatment	105	D2	48*	2	102	1	--	--	2
Follow-up	110	D60	1440	2	103	1	3	202	5
* 48hr sample taken prior to the end of infusion. . If the infusion was discontinued earlier than the complete 48 hour infusion due to whatever the reason, the 48 hour PK serum sample will be collected just prior to the end of infusion if possible and time of collection should be recorded.									

[redacted]