NOVARTIS

Clinical Development

RLX030/Serelaxin

Study No. CRLX030A2208 / NCT02151383

Multicenter, open-label, dose escalation study to evaluate safety, tolerability and pharmacokinetics of RLX030 in addition to standard of care in pediatric patients from birth to <18 years of age, hospitalized with acute heart failure

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List of abbreviations

AE	Adverse event
AHA	American heart association
AHF	Acute heart failure
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUCinf	Area under the serum concentration-time curve from time zero to infinity
AUClast	Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration point
AV	atrio-ventricular
BG	Blood gasses
bid	Twice a day
BP	Blood pressure
BUN	Blood urea nitrogen
cAMP	Cyclic adenosin monophosphate
C_{dyn}	Dynamic lung compliance
CFR	US Code of Federal Regulations
CHBP	Child-bearing potential
CL	Clearance
CPO	Country Pharma Organization
CRF	Case report form
CRO	Contract Research Organization
Css	Steady-state concentration
CV	Cardiovascular
CVP	Central venous pressure
DBP	Diastolic blood pressure
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate

[redacted]

EMR	Electronic Medical Record
$ETCO_2$	End-tidal CO_2
FiO_2	Inspired oxygen fraction
GCP	Good Clinical Practice
HF	Heart failure
HR	Heart rate
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
iv	Intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
LAP	Left atrial pressure
LFT	Liver function test (raised serum transaminases and/or bilirubin levels)
LVEF	Left ventricular ejection fraction
LVEDD	Left ventricular end-diastolic dimensions
LVESD	Left ventricular end-systolic dimensions
LVFS	Left ventricular fractional shortening
LVOTO	Left ventricular outflow tract obstruction
MAP	Mean airway pressure
MedDRA	Medical dictionary for regulatory activities
OC/RDC	Oracle Clinical/Remote Data Capture
od	Once a day
p_aO_2	Arterial oxygen partial pressure
PALS	Pediatric advanced life support
PAP	Pulmonary artery pressure
PEEP	Positive end-expiratory pressure
PIP	Peak inspiratory pressure
po	Oral(ly)
PK	Pharmacokinetic
RR	Respiratory rate
RRT	Renal replacement therapy

[redacted]

RXFP1	Relaxin family peptide receptor 1
SAE	Serious adverse event
SBP	Systolic blood pressure
S_aO_2	Arterial oxygen saturation
S_pO_2	Pulse oximetry
$S_{cv}O_2$	Central venous oxygen saturation
SOC	Standard of care
SUSAR	Suspected Unexpected Serious Adverse Reactions
T1/2	Terminal phase half-life
T3	Tracking, Trajectory, Trigger Software technology from Etiometry™
$TcCO_2$	Transcutaneous CO_2
TCPC	Total cavo-pulmonary connection procedure
ULN	Upper limit of normal
VAD	Ventricular assist device
VAS	Visual analog scale
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

[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 system
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.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Period	A subdivision of a cross-over study
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all investigational/study treatment administration and all assessments (including follow-up)
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 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

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Protocol synopsis

Protocol number	CRLX030A2208
Title	Multicenter, open-label, dose escalation study to evaluate safety, tolerability and pharmacokinetics of RLX030 in addition to standard of care in pediatric patients from birth to <18 years of age, hospitalized with acute heart failure
Brief title	PK and safety of serelaxin when added to standard of care in pediatric patients hospitalized with acute heart failure
Sponsor and Clinical Phase	Novartis/Phase II
Investigation type	Biologic
Study type	PK and safety
Purpose and rationale	The purpose of this open-label, dose escalation study is to evaluate safety, tolerability and pharmacokinetics of 48 hour iv serelaxin (RLX030) infusion in addition to standard of care (SOC) therapy in pediatric patients from birth to <18 years of age, who are hospitalized with AHF. [redacted]
Primary Objectives	**Primary Objectives** • To evaluate the safety and tolerability of an iv serelaxin infusion in addition to standard of care in hospitalized pediatric patients with AHF • To investigate the effects of age on the pharmacokinetics of serelaxin given as iv infusion in addition to standard of care in hospitalized pediatric patients with AHF
Secondary Objective	**Secondary objective** To evaluate the hemodynamic effects of different doses of serelaxin given as an iv infusion in addition to standard of care in hospitalized pediatric patients with AHF (efficacy parameters: arterial blood pressure,), left atrial pressure (LAP), pulmonary artery pressure (PAP – systolic and diastolic) central venous and arterial oxygen saturation, urine output, and blood lactate levels)
Study design	This is a multicenter, open-label, dose-escalation study to evaluate the safety, tolerability and pharmacokinetics of RLX030 in addition to standard of care in pediatric patients from birth to <18 years. A fixed dose titration scheme will be used for this study. A total duration of 48 hours is planned for the constant iv serelaxin infusion with dose escalations every 16 hours. A low-dose group and a high-dose group will be enrolled sequentially in every age cohort. During this 48-hour treatment period, the serelaxin dose rates to be administered are 3 µg/kg/day, 10 µg/kg/day and 30 µg/kg/day in the low-dose group; 10 µg/kg/day, 30 µg/kg/day and 100 µg/kg/day in the high-dose group. These dose rates are anticipated to be safe in the pediatric population and are based on the dose range investigated in adults with AHF.

[redacted]

	A minimum of 30 male or female pediatric patients will be enrolled in this study with 3 patients in each low-dose group for age cohorts 1, 2, 3 and 4; and 6 patients in each high-dose group for age cohorts 3 and 4, and 3 (maximum 6) patients in each high-dose group for age cohorts 1 and 2. The four age cohorts are as follows: • Cohort 1: 6 to <18 years [3 low-dose patients, 3 high-dose patients (maximum 6)] • Cohort 2: 1 to <6 years [3 low-dose patients, 3 high-dose patients (maximum 6)] • Cohort 3: infants 1 month to <1 year [3 low-dose patients, 6 high-dose patients] • Cohort 4: neonates birth to <1 month [3 low-dose patients, 6 high-dose patients] Age cohorts will be enrolled sequentially from age cohort 1 to 4, within each dose group. For each age cohort, patients will be enrolled first into the low-dose group and if it is considered safe after a review of all available safety and pharmacokinetic (PK) data, up to and including study day 5, then patients will be enrolled into the low-dose group for the succeeding age cohort. Patients cannot be enrolled into the high-dose group for a given age cohort until data from the low-dose group of that same age cohort and the high-dose group of the preceding age cohort (where present) has been reviewed and it is considered safe to proceed.
Population	The study population will consist of 30 male or female pediatric patients (birth to <18 years of age) hospitalized with the following: signs and symptoms of AHF who have a requirement for a stable dose of vasoactive and/or inotropic agents and, in patients with medical etiologies of AHF, echocardiographic evidence of reduced ventricular function. Both, medical and post-surgical [redacted] etiologies of AHF can be included in the study. [redacted]
Key Inclusion criteria (see protocol for full details)	1. Male or female, [redacted], with body weight ≥2.5 kg to ≤120 kg 2. Hospitalized in an intensive/critical care unit or continuously monitored step-down unit with the following: a. signs and symptoms of AHF of any etiology and b. a stable dose of vasoactive and/or inotropic agents [redacted] c. [redacted]

[redacted]

	[redacted] 3. Systolic blood pressure (SBP) consistently equal to or greater than the calculated 25th percentile SBP for age and gender as described in the protocol. 4. Stable pulmonary function, i.e. patient is extubated or is stable on ventilator support.
Key Exclusion criteria (see protocol for full details)	1. Hypovolemia 2. Moderate to severe left ventricular outflow tract (including sub-valvular, valvular and supra-valvular), mitral stenosis or aortic arch obstruction 3. Patients with single ventricle physiology before their Fontan operation (However, single ventricle patients post Glenn operation before their Fontan/Total cavo-pulmonary connection procedure (TCPC) can be enrolled.) 4. Patients on ECMO or VAD 5. Patients with fixed pulmonary hypertension (i.e. ≥6 Wood Units, unable to reduce <6 Wood Units with medical therapy) 6. Patients with blood lactate levels >5 mmol/L at the time of enrollment 7. Birth < 36 weeks post-conceptual age (applies only to children <1year old at baseline) 8. Confirmed or clinically suspected systemic infection (sepsis) or severe localized infection requiring iv antibiotics 9. Dyspnea or acute lung injury primarily due to non-cardiac causes 10. Patients with severe renal impairment; those known to have significant renal disease and those having current or planned renal replacement therapy 11. Excessive use of inotropic and/or vasoactive agents at screening [vasoactive score >20 (Davidson et al. 2012): dose of dopamine + dobutamine + (epinephrine x 100) + (norepinephrine x 100) + (phenylephrine x 100) + (milrinone x 10) + (vasopressin x 10,000)] 12. Current or planned use of the following concomitant medication during the duration of the study drug infusion: levosimendan,

[redacted]

	nesiritide 13. Planned surgery <48 hours after screening 14. Patients with uncorrected coronary abnormalities that predisposes them for myocardial ischemia 15. History or current diagnosis of cardiac electrocardiographic abnormalities indicating significant risk of safety for patients participating in the study such as: 16. Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block, unless they are successfully managed with a pacemaker or anti-arrhythmic medication 17. History of familial long QT syndrome or known family history of Torsades de Pointes 18. Any major solid organ transplant recipient within 1 year of transplantation 19. Any major solid organ transplant recipient who presents with severe organ rejection 20. 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 21. Females of child-bearing potential (girls who have reached menarche), unless they are using highly effective methods of contraception during dosing of study treatment and for the duration of the study 22. Any clinically significant bleeding that occurs after screening and prior to infusion of study drug 23. Any indication of clinical instability, based on the investigator's judgement, preceding enrollment and/or prior to the infusion of study drug
Investigational and reference therapy	Serelaxin is administered in a continuous iv infusion for a total of 48 hours. Dose rates of 3 µg/kg/day, 10 µg/kg/day and 30 µg/kg/day in the low-dose group; 10 µg/kg/day, 30 µg/kg/day and 100 µg/kg/day in the high-dose group will be used.
Efficacy assessments	The hemodynamic effects of different doses of serelaxin will be assessed at baseline, prior to each dose escalation and at approximately 24 hours after the end of the infusion, as a secondary objective. The following hemodynamic measurements will be assessed (as available): arterial BP and central venous pressure (CVP), left atrial pressure (LAP), pulmonary artery pressure (PAP – systolic and diastolic), central venous and arterial oxygen saturation, urine output, and blood lactate levels. (Note: Hemodynamic effects will also be assessed for safety at additional time points during the study as outlined in the protocol.)
Safety assessments	• Physical Exam • Vital signs, respiratory parameters and clinical assessments (including hemodynamic effects) • Laboratory evaluations

[redacted]

	• ECG • Adverse events/SAEs
Other assessments	[redacted]
Data analysis	The PK parameters Css and CL will be mainly summarized descriptively by age cohort and dose within each dose group. A graphical presentation will be employed to show mean and individual RLX030 concentration-time profiles for each age cohort and each dose group. [redacted] Safety data including adverse events, laboratory, vital signs and ECG data will be summarized by age cohort and dose group and for all patients as appropriate as well. Hemodynamic assessments will be also provided by age cohort and dose group and for all patients. [redacted]
Key words	Acute Heart Failure, Pediatrics, Congenital Heart Disease, Cardiomyopathy

[redacted]

1 Introduction

1.1 Background

Heart failure (HF) has been defined as "constellation of structural and functional abnormalities, elevated filling pressures, neurohormonal activation, and signs and symptoms" (Kim JJ et al. 2008). It is, in many ways, a much more heterogeneous disease in children than it is in adults. First, the classical signs and symptoms observed in adults with HF such as exertional dyspnea, pitting edema or jugular venous pulsation, are often absent (or difficult to detect) in children depending on their age and underlying disease. Second, there is a multitude of etiologies of pediatric HF (see Table 1-1) which contrasts with HF in the adult population. Third, there are multiple mechanistic factors that can lead to cardiac failure including 1) decreased contractility (e.g. cardiomyopathy, sepsis, myocarditis, post-surgical low cardiac output syndrome), 2) volume overload (e.g. pulmonary hypercirculation secondary to left-to-right shunts, valvular regurgitations), 3) pressure overload (e.g. sub-valvular or valvular stenosis, or supra-valvular obstructions like coarctation of the aorta), 4) diastolic dysfunction (e.g. tetralogy of Fallot, myocardial stunning) or 5) changes in systemic or pulmonary vascular resistance (e.g. primary or idiopathic pulmonary hypertension, systemic hypertension) (Epstein and Wetzel 2006). HF in children can be a transient problem, for example after open heart surgery and cardiopulmonary bypass for congenital heart disease, can follow a more protracted course with bouts of acute decompensations (similar to adult heart failure) or lead to terminal HF and death. Patients with terminal HF may be eligible for cardiac transplantation and may benefit from mechanical support (Extracorporeal Membrane Oxygenation [ECMO] or Ventricular Assist Device [VAD]) as a bridging therapy.

Table 1-1 Causes of heart failure in children and adolescents

Rhythm disorders
- Brady- or tachy- arrhythmias
- Lack of AV synchrony

Volume overload
- Intracardiac shunts (congenital heart disease)
- Extracardiac shunts (e.g. AV malformation, aneurysm of vein of Galen)
- Valvular regurgitation (congenital, endocarditis, traumatic, rheumatic fever)

Pressure overload
- Cardiac obstruction (valvular or intracardiac abnormalities, congenital or acquired)
- Extracardiac obstruction (coarctation of aorta, pulmonary hypertension, embolism, hypertension)

Cardiomyopathies – systolic or diastolic dysfunctions
- Hypoxia
- Post-open heart surgery (post-bypass low cardiac output syndrome)
- Myocarditis (viral or bacterial)

[redacted]

- Metabolic disorders
  - Hypoglycemia
    - Hypocalcemia and Vitamin D deficiency
    - Acidosis
    - Hypothyroidism
    - Hypothermia
    - Glycogen storage disease
    - Carnitine deficiency
    - Mucopolysaccharidoses
    - Endomyocardial fibroelastosis
- Familial dilatative cardiomyopathy
- Hypertrophic cardiomyopathy
- Cardiac trauma
- Duchenne's muscular dystrophy
- Friedreich's ataxia
- Drug intoxication or toxicity (chemotherapy)
- Sickle cell disease
- Coronary disease
  - Anatomic anomalies of the coronaries (implantation or trajectory)
  - Kawasaki's disease
  - Polyarteritis nodosa

High cardiac output failure

- Sepsis
- Thyrotoxicosis
- Severe anemia
- Liver failure

Reference: modified from Barry 2010

Etiologies of HF are age dependent with hypoxia, AV malformations, congenital heart disease (CHD, and related surgery), myocarditis and tachyarrhythmias being the most common in neonates, congenital heart disease (and related surgery), AV malformations, anomalous coronary arteries, metabolic cardiomyopathies, tachyarrhythmias, Kawasaki's disease and acute hypertension (haemolytic uremic syndrome) seen most frequently in infants and toddlers and rheumatic fever, hypertension (glomerulonephritis), myocarditis, endocarditis, cor pulmonale (cystic fibrosis), drug toxicity (radiation, doxorubicin, anthracycline) and thyrotoxicosis as well as cardiomyopathy most commonly seen in older children and adolescents (Madriago 2010).

The overall incidence and prevalence of pediatric HF (acute and chronic) is unclear, largely because there is no accepted universal classification applied to its many forms. The largest HF burden comes from children born with congenital malformations, which occurs in approximately 8 per 1000 live births of which 1-2 per 1000 develop HF (Kay 2001). Although cardiomyopathy is relatively rare (around 1 per 100,000 children according to Lipshultz 2003 and Nugent 2003), approximately 40% of patients who experience cardiomyopathy develop HF of such severity that it leads to transplantation or death (Madriago 2010). Overall, a HF incidence of 10.4% has been reported in patients <16 years with heart disease (congenital or

[redacted]

acquired – Massin 2008) and a 2 to 7.7/100,000 incidence of HF in the general pediatric population (Tseng 2010, Neumann 2009), with the highest incidence in infants and children between 0 and 4 years old (21.7/100,000).

The clinical manifestation of acute heart failure (AHF) depends on the age of the patient. In children and adolescents, signs and symptoms are similar to the ones observed in adults, namely fatigue, exercise intolerance, dyspnea and orthopnea. Peripheral edema, pulmonary rales and increased jugular venous pressure might be difficult to detect in smaller children but are more commonly present in older children and adolescents. Abdominal pain can be a prominent feature. Heart failure might be more difficult to diagnose in newborns and infants. Prominent manifestations include central cyanosis, tachypnea, tachycardia, poor feeding, excessive perspiration, poor weight gain, irritability and weak cry. Signs of increased work of breathing (retractions, nasal flaring, wheezing, grunting), venous stasis (hepatosplenomegaly, ascites, rarely edema) and poor peripheral perfusion (mottling, cool extremities, delayed capillary refill, gastrointestinal symptoms) can be detected but rales might be difficult to hear on auscultation (Kantor 2010).

Current standard of care (SOC) of AHF includes, almost always, diuretics, oxygen and potentially iv vasoactive substances like vasodilators (e.g. sodium nitroprusside, nipride), inotropes (levosimendan or more commonly catecholamines like dopamine, epinephrine) or inodilators (e.g. milrinone, dobutamine). Ventilatory support (continuous positive airway pressure or invasive mechanical ventilation) can help with gas exchange in the congested lung and reduction of left ventricular afterload. Mechanical circulatory support (ECMO or VADs) can be indicated in severe cases and heart transplant might be needed for terminal HF. The goals of AHF therapy, in paediatric patients as in adults, is to stabilize the patient's vital functions, diagnose and treat underlying causes if possible and transition to outpatient therapy (Kantor 2010, Kantor 2010a).

Relaxin (H2) is a naturally occurring peptide hormone that has been associated with many of the maternal hemodynamic and renovascular adjustments in response to the demands of pregnancy, such as dilation of systemic and renal blood vessels and increase in global arterial compliances (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). It is known that nitric oxide, endothelial endothelin type B receptor, vascular endothelial growth factor (VEGF) and cAMP act as mediators for the vasodilatory as well as other anti-fibrotic and anti-inflammatory effects of relaxin (Bani et al 1998; Danielson et al 1999; Dschietzig et al 2003; Du et al 2010). [redacted]

[redacted]

[redacted]

Serelaxin is a recombinant protein identical in structure to the naturally occurring H2 relaxin. Its efficacy and safety in adult AHF patients as a continuous 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 2009) and the phase III pivotal study RELAX-AHF (Teerlink 2013).

[redacted]

The purpose of this study is to provide pharmacokinetic and short-term safety information in the pediatric patient population from birth to <18 years of age.

[redacted]

[redacted]

1.2 Purpose

The purpose of this open-label, dose escalation study is to evaluate safety, tolerability and pharmacokinetics of an iv serelaxin (RLX030) infusion in addition to standard of care (SOC) therapy in pediatric patients from birth to <18 years of age, who are hospitalized with AHF.

[redacted]

2 Study objectives

2.1 Primary objectives

- To evaluate the safety and tolerability of an iv serelaxin infusion in addition to standard of care in hospitalized pediatric patients with AHF
- To investigate the effects of age on the pharmacokinetics of serelaxin given as iv infusion in addition to standard of care in hospitalized pediatric patients with AHF

2.2 Secondary objective

- To evaluate the hemodynamic effects of different doses of serelaxin given as an iv infusion in addition to standard of care in hospitalized pediatric patients with AHF (efficacy parameters: arterial blood pressure, left atrial pressure (LAP), pulmonary artery pressure (PAP – systolic and diastolic), central venous and arterial oxygen saturation, urine output, and blood lactate levels)

2.3 Exploratory objectives

[redacted]

3 Investigational plan

3.1 Study design

This study uses an open-label, dose escalation design in order to evaluate safety, tolerability and pharmacokinetics of RLX030 in addition to standard of care in pediatric patients from birth to <18 years. Hospitalized patients in an intensive/critical care unit or a continuously monitored step-down unit with the following criteria will be screened for inclusion:

[redacted]

1. signs and symptoms of AHF and
2. a requirement for a stable dose of vasoactive and/or inotropic agents [defined as a 2-hour period without major changes (i.e. >20% increase/decrease) in the infusion rate] and
3. echocardiographic evidence of reduced ventricular function

The same criteria apply for patients after open heart surgery except criterion number 3. (echocardiographic evidence of reduced ventricular function). Post-operative patients can only be included ≥6 hours after surgery for patients 0 to <1 year old and ≥12 hours after surgery for patients 1 to <18 years old. Patients who present with AHF following open heart surgery until 1 month after the intervention are considered post-operative patients for the purpose of this study. Echocardiographic examination within 24 hours prior to enrollment can be considered as the screening examination, including the trans-esophageal or trans-thoracic echocardiography in the immediate post-operative period. The screening echocardiographic examination in post-surgical patients is to be performed after completion of the surgery in a hemodynamically stable patient.

If a patient is found to be eligible for study entry during screening and at the baseline evaluation, the patient will enter the study and can start the 48-hour treatment period. Study participants will be assessed daily to day 5, at day 14 and at day 28 (telephone contact) (see Table 6-1 for details. Patients will be followed for serious adverse events for 30 days after completion or discontinuation from the study and all serious adverse events occurring within this time frame are to be reported to Novartis (see Section 7.2.2).

[redacted] A total duration of 48 hours is planned for the constant iv serelaxin infusion with dose escalations every 16 hours. A low-dose group and a high-dose group will be enrolled sequentially in every age cohort. During this 48-hour treatment period, the serelaxin dose rates to be administered are 3 µg/kg/day, 10 µg/kg/day and 30 µg/kg/day in the low-dose group; 10 µg/kg/day, 30 µg/kg/day and 100 µg/kg/day in the high-dose group [redacted] These dose rates are anticipated to be safe in the pediatric population and are based on the dose range investigated in adults with AHF.

Thirty (30) male or female pediatric patients (minimum) will be enrolled in this study with 3 patients in each low dose group for age cohorts 1, 2, 3 and 4; and 6 patients in each high-dose group for age cohorts 3 and 4, and 3 (maximum 6) patients in each high dose group for age cohorts 1 and 2. The four age cohorts are as follows:

- Cohort 1: 6 to <18 years [3 low-dose patients, 3 high-dose patients (maximum 6)]
- Cohort 2: 1 to <6 years [3 low-dose patients, 3 high-dose patients (maximum 6)]
- Cohort 3: infants 1 month* to <1 year [3 low-dose patients, 6 high-dose patients]
- Cohort 4: neonates birth to <1 month* [3 low-dose patients, 6 high-dose patients]

*1 month = 30 days

[redacted]

Age cohorts will be enrolled sequentially from age cohort 1 to 4, within each dose group. For each age cohort, patients will be enrolled first into the low-dose group and if it is considered safe after a review of all available safety and pharmacokinetic (PK) data, up to and including study day 5, then patients will be enrolled into the low-dose group for the succeeding age cohort. Patients cannot be enrolled into the high-dose group for a given age cohort until data from the low-dose group of that same age cohort and the high-dose group of the preceding age cohort (where present) has been reviewed and it is considered safe to proceed. [redacted]

Enrollment within each dose group will be temporarily stopped 4 times for the low dose group and 3 times for the high dose group during the study for a review of safety and PK data as follows:

Low Dose Group

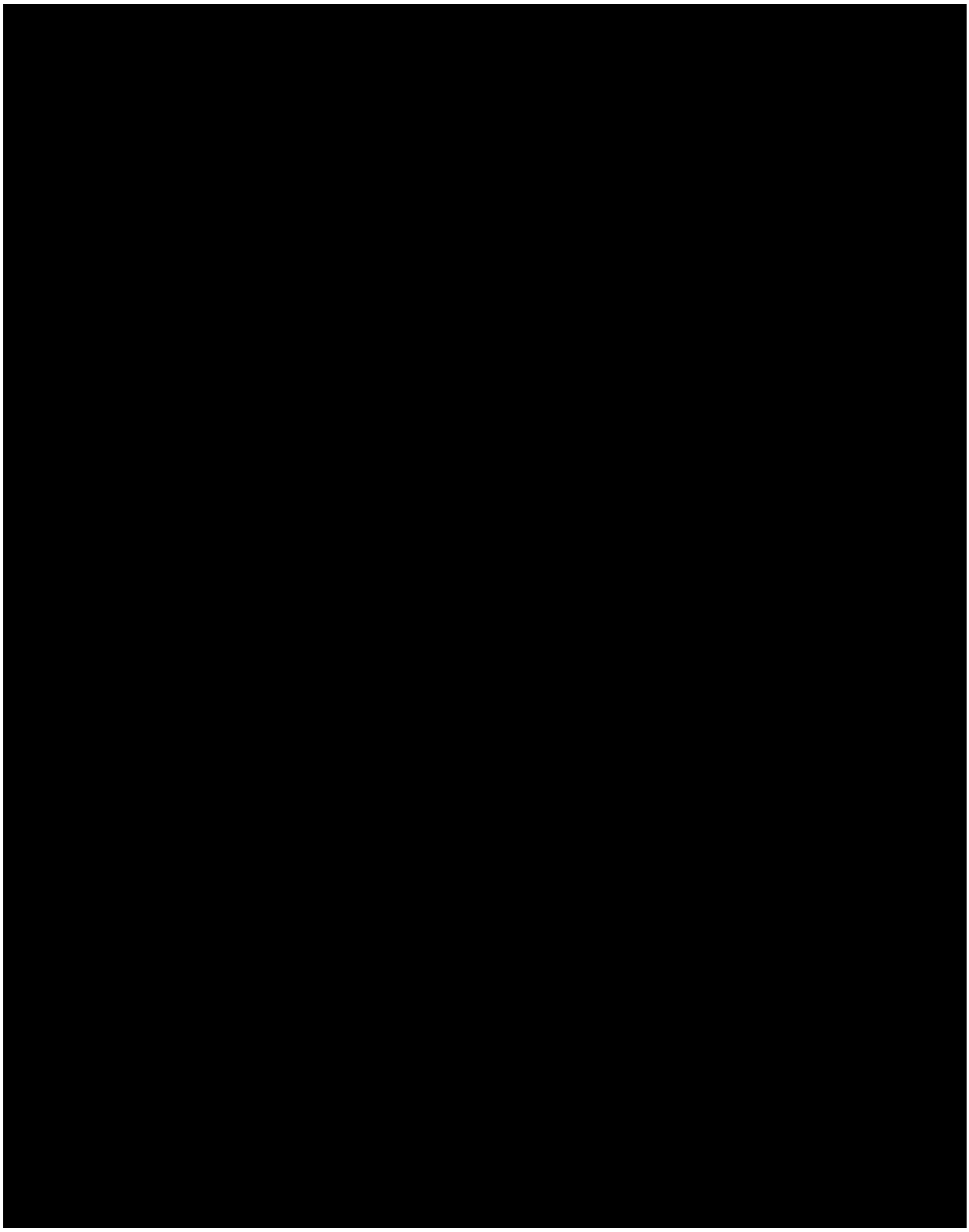
- 1st enrollment stop for low-dose, safety and PK data review after completion (up to day 5) of 3 low-dose patients in age cohort 1
- 2nd enrollment stop for low-dose, safety and PK data review after completion (up to day 5) of 3 low-dose patients in age cohort 2
- 3rd enrollment stop for low-dose, safety and PK data review after completion (up to day 5) of 3 low-dose patients in age cohort 3
- 4th enrollment stop for low-dose, safety and PK data review after completion (up to day 5) of 3 low-dose patients in age cohort 4.

High Dose Group

- 1st enrollment stop for high-dose safety and PK data review after completion (up to day 5) of 3 high-dose patients in age cohort 1
- 2nd enrollment stop for high-dose, safety and PK data review after completion (up to day 5) of 3 high-dose patients in age cohort 2
- 3rd enrollment stop for high-dose, safety and PK data review after completion (up to day 5) of 6 high-dose patients in age cohort 3

Note: For a given age cohort, high-dose patients can only be enrolled after 3 low-dose patients have been enrolled in that age cohort and 3 patients have been enrolled in the high-dose group of the preceding age cohort (as applicable), and their safety and PK data reviewed, and it is considered safe to proceed. For any additional high-dose group, age cohort 1 or 2 patients (i.e. beyond the 3 required patients), their data will be reviewed at the next available PSRC meeting.

[redacted]



[redacted]

3.2 Rationale of study design

This first open-label study in pediatric patients from birth to <18 years, hospitalized with AHF, is designed to evaluate the safety, tolerability and pharmacokinetics of escalating doses of serelaxin [redacted] Qualifying study participants will receive serelaxin during the hospitalization in addition to SOC therapy for AHF according to local guidelines or institutional standards. [redacted]

[redacted]

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

[redacted]

3.4 Rationale for choice of comparator

Not applicable

3.5 Purpose and timing of interim analyses/design adaptations

[redacted]

3.6 Risks and benefits

In adults, hospitalization and worsening heart failure with accompanying end organ damage, such as worsening renal function and myocardial injury, are both associated with increased mortality. In two adult AHF studies (pre-RELAX-AHF, Teerlink et al, 2009 and RELAX-AHF, Teerlink et al, 2013) a 48 hour serelaxin infusion on top of SOC led to a significant relieve of dyspnea and congestion, the presenting elements of AHF in adults, compared to placebo on top of SOC. This was associated with a significant reduction in early worsening of HF (defined as intensification of HF therapy) and length of (index) hospitalization and intensive care unit stay [redacted]

Overall, serelaxin (on top of SOC) was well-tolerated with an adverse event profile comparable to placebo (on top of SOC). Although slightly more hypotension-related adverse events were reported in the serelaxin treatment arm versus placebo due to its vasodilatory effects, without a dose-response or exposure-response relationship, the use of stringent blood pressure inclusion criteria and the management of blood pressure decreases during serelaxin

[redacted]

infusion (i.e. mandated 50% dose reduction and/or discontinuation if pre-specified blood pressure decreases were met) have demonstrated that serelaxin-induced hypotensive effects were generally mild and easily manageable without causing harm and the majority of patients were able to stay on drug.

[redacted]

several safeguards are included in the CRLX030A2208 study design in order to reduce the risk in this new patient population as much as possible. First, a low-dose group, dosed at 3, 10 and 30 µg/kg/day (within-patient dose escalation every 16 hours) will be enrolled ahead of every high-dose group, which is dosed at 10, 30 and 100 µg/kg/day (also within-patient dose escalation every 16 hours). The high-dose group will only be enrolled if the review of safety and PK data (up to day 5) from the low-dose group shows that it is safe to do so. Second, age cohorts will be enrolled sequentially and younger age cohorts will only be allowed into the study once the review of safety and PK data (up to day 5) from the preceding older age cohort shows that it is safe to do so. Third, the risk to the patient will also be minimized by compliance with the inclusion/exclusion criteria that aim to recruit patients with mild to moderate hemodynamic impairment, excluding the sickest and most vulnerable individuals in this population.

Female patients of child bearing potential should be informed that taking the study drug may involve unknown risks to the fetus, if pregnancy were to occur during the study. Informed consent (and assent where required) that outlines the risks as well as protocol specific safety rules to adhere to the contraception requirements for the duration of the study has to be signed. In the case of any concerns regarding compliance with these requirements the patient should be excluded or discontinued from the study. In addition, females of child bearing potential

[redacted]

[redacted] are required to have a negative serum pregnancy test before entering the study.

Refer to the IB for additional information regarding the safety profile of serelaxin.

[redacted]

4 Population

The study population will consist of a minimum of 30 male or female pediatric patients (birth to <18 years of age) hospitalized with the following: signs and symptoms of AHF who have a requirement for a stable dose of vasoactive and/or inotropic agents and, in patients with medical etiologies of AHF, echocardiographic evidence of reduced ventricular function. Both, medical and post-surgical [redacted] etiologies of AHF can be included in the study.

[redacted]

4.1 Inclusion criteria

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

1. Written informed consent by parent(s)/legal guardian(s) for the pediatric patient must be obtained before any study-specific assessment is performed[redacted]. A consent or assent may also be required for some patients depending upon their age and local requirements
2. Male or female, [redacted], with body weight ≥2.5 kg to ≤120 kg (basis for inclusion criteria weight: pre-operative weight for post-operative patients and weight on hospital admission for non-surgical patients)
3. Hospitalized in an intensive/critical care unit or continuously monitored step-down unit with the following:
    a) signs and symptoms of AHF of any etiology[redacted] and
    b) a stable dose of vasoactive and/or inotropic agents[redacted]
    c) [redacted]

[redacted]

[redacted]

4. Systolic blood pressure (SBP) consistently equal to or greater than the calculated 25th percentile SBP for age and gender per Appendix 3. [redacted]
5. Stable pulmonary function, i.e. patient is extubated or is stable on ventilator support.

[redacted]

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. Hypovolemia
2. Moderate to severe left ventricular outflow tract (including sub-valvular, valvular and supra-valvular), mitral stenosis or aortic arch obstruction (evidence of peak gradient ≥40 mmHg on echocardiographic or BP measurements)
3. Patients with single ventricle physiology before their Fontan operation (However, single ventricle patients post Glenn operation before their Fontan/Total cavo-pulmonary connection procedure (TCPC) can be enrolled.)
4. Patients on ECMO or VAD (excluded because of the potential interference of the extracorporeal circuit with the PK profile of serelaxin)
5. Patients with fixed pulmonary hypertension (i.e. ≥6 Wood Units, unable to reduce <6 Wood Units with medical therapy)
6. Patients with blood lactate levels >5 mmol/L at screening (excluded because of the possibility of a compensated shock)
7. Birth < 36 weeks post-conceptual age (applies only to children <1year old at baseline)
8. Confirmed or clinically suspected systemic infection (sepsis) or severe localized infection requiring iv antibiotics

[redacted]

9. Dyspnea or acute lung injury primarily due to non-cardiac causes
10. Patients with severe renal impairment, those known to have significant renal disease (e.g. significant renal dysplasia) and those having current or planned renal replacement therapy [Severe renal impairment is defined in cohort 1 to 3 as eGFR <30 mL/min/1.73m^2 (Hogg et al. 2003), calculated using the modified Schwartz formula (eGFR = 0.41 x height (cm)/Scr (mg/dl) - Schwartz et al. 2009) and in cohort 4 as urine output <0.5mL/kg/hour for the 24 hours prior to screening, or anuria for the 12 hours prior to screening (derived from the neonatal RIFLE criteria; Ricci 2013).]
11. Excessive use of inotropic and/or vasoactive agents at screening [vasoactive score >20; Davidson et al. 2012: dose of dopamine + dobutamine + (epinephrine x 100) + (norepinephrine x 100) + (phenylephrine x 100) + (milrinone x 10) + (vasopressin x 10,000)]
12. Current or planned use of the following concomitant medications during the duration of the study drug infusion: levosimendan, nesiritide
13. Planned surgery <48 hours after screening
14. Patients with uncorrected coronary abnormalities that predispose them for myocardial ischemia
15. History or current diagnosis of cardiac electrocardiographic abnormalities indicating significant risk of safety for patients participating in the study such as:
    - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block, unless they are successfully managed with a pacemaker or anti-arrhythmic medication
    - History of familial long QT syndrome or known family history of Torsades de Pointes
16. Any major solid organ transplant recipient within 1 year of transplantation
17. Any major solid organ transplant recipient who presents with severe organ rejection
18. 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
19. Severe malnutrition
20. Post-operative bleeding >5 mL/kg/hour for ≥2 consecutive hours at any time 4 hours prior to screening
21. Any advanced, severe or unstable disease that may interfere with the primary or secondary study outcome evaluations or put the patient at special risk
22. 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

[redacted]

23. Females of child-bearing potential (girls who have reached menarche), unless they are using highly effective methods of contraception during dosing of study treatment and for the duration of the study. Highly effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

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

    Note: In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the respective ICF.

24. Use of other investigational drugs within 30 days or 5 half-lives prior to screening, whichever is longer
25. History of hypersensitivity to serelaxin or to drugs of similar chemical classes
26. History of previous serelaxin administration
27. Inability of the patient or the parents/legal guardians to follow instructions or comply with follow-up procedures
28. 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.
29. Any clinically significant bleeding that occurs after screening and prior to infusion of study drug
30. Any indication of clinical instability, based on the investigator's judgement, preceding enrollment and/or prior to the infusion of study drug

[redacted]

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

Escalating doses of serelaxin will be administered in a continuous iv infusion for a total of 48 hours. Dose rates of 3 µg/kg/day, 10 µg/kg/day and 30 µg/kg/day will be used in the low-dose group and dose rates of 10 µg/kg/day, 30 µg/kg/day and 100 µg/kg/day will be used in the high-dose group. [redacted]

5.2 Additional study treatment

No additional treatment beyond the investigational treatment is required for this trial. However, patients in this study will all be required to receive SOC management of AHF during both hospitalization and after discharge according to the regional or local guidelines and/or institutional standard.

5.3 Treatment arms

All enrolled patients will receive serelaxin in this open–label study.

5.4 Treatment blinding

Not applicable for this open-label study.

[redacted]

5.5 Treating the patient

5.5.1 Patient numbering

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

Upon signing the informed consent form, the patient is assigned the next sequential number as given by the investigator using the next blank eCRF book available from the electronic data capture (EDC) system. [redacted]

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with open label study medication.

The investigational treatment packaging has a 2-part label. A unique medication number is printed on each part of this label. [redacted]

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

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

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the investigational treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment [redacted]

[redacted]

[redacted]

5.5.3.2 Handling of other study treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

The study drug infusion will begin after informed consent has been given in writing (ICF signed by parent/guardian and patient consent or assent where applicable) and the completion of all screening/baseline procedures, and will continue for a total 48 hours (16 hour infusion per dose level). The study drug should be administered via a peripheral or central iv line or port, as soon as possible, but no more than 5 hours after enrollment (i.e. confirmation of eligibility for the study and the baseline IRT contact where a medication number is assigned). Compatible filters and syringes which have been tested and qualified for use with serelaxin, must be used to prepare and administer the study drug. [redacted]

The required amount of study drug will be calculated for each patient for each dose titration level and will be withdrawn from the 6 mL vials (with 3.5 mL fill) contained in the study drug kits, added to a syringe of 5% dextrose solution (10% dextrose may also be considered), and then infused at a constant rate over a period of 16 hours for each titration level. [redacted]

Each dose level is infused over 16 hours. Dose escalation should only occur if

- the patient does not fulfill any requirement for dose adjustment or discontinuation (see Section 5.5.5 Permitted dose adjustments of study treatment) on the preceding infusion rates, and
- the investigator considers dose escalation to be safe based on his global clinical assessment, including an evaluation of the patient's hemodynamic status (including physical examination (Section 6.5.1), vital signs and hemodynamic parameters, arterio-venous oxygen extraction) and a comparison of his/her current condition with the one before starting serelaxin and before the previous dose escalation.

If the investigator considers it unsafe, based on his/her global clinical assessment, to increase the serelaxin dose to the next dose level the patient should remain on the same dose level for another 16 hours (if tolerated). At the end of this 16 hour period, another global clinical assessment must be done to determine whether or not it is safe to escalate the dose. If it is deemed safe at that time, the dose is increased to the next dose level in the sequence of the assigned dose group (i.e. low-dose or high-dose group), not the initially planned dose level, for the remainder of the 48 hour infusion time. For example, if a patient receives 3µg/kg/day for 16 hours and a decision is taken to that the patient should *not* be up-titrated to the next dose level, they are to be dosed at 3µg/kg/day for another 16 hours, if tolerated. If after the second 16 hours at 3µg/kg/day, a decision is taken to up-titrate the patient, they would then

[redacted]

receive a 10µg/kg/day, for 16 hours, again if tolerated. The total infusion time of serelaxin should not exceed 48 hours regardless of dose titration. All assessments, including PK sampling, should continue per protocol even if the dose rate is not escalated.

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

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 of study treatment

This section describes the actions that are required if a systolic BP decrease (i.e. <5th percentile for age) occurs during the administration of study drug and is confirmed by two measurements taken 10 minutes apart (in patients with intermittent BP measurements) or by a consistent measurement over ≥5 min (in patients with invasive continuous BP measurements). This event is considered a "systolic blood pressure decrease event" (SBPDE) and must be recorded as such on the appropriate eCRF.

If the SBP falls to <5th percentile for the age of the patient (AHA PALS guidelines 2010, Kleinman 2010, see Appendix 4) and is a confirmed SBPDE per the criteria in the previous paragraph, then the following steps are required:

1) In all patients:

   Assess the patient and treat alternative causes of hypotension (consider hypovolemia, arrhythmia, heart-lung interactions, concomitant medications, pneumothorax or pericardial tamponade, hardware malfunction or measuring error etc.)

2) As clinically indicated, the following steps should be taken, preferentially in the indicated order (however, the options can be applied in sequence or separately at the investigator's discretion):

   1. Increase the infusion rate of inotropic and/or vasoactive drugs as clinically indicated up to a vasoactive score of 20 and/or
   2. Reduce the serelaxin infusion rate by 50% and/or
   3. Discontinue serelaxin infusion

Patients who tolerate the reduced serelaxin infusion rate should remain on this reduced infusion rate for the remainder of the 48 hour infusion period, as tolerated. The exact time and date of the reduction of the study drug infusion rate must be recorded on the Drug Administration Record case report form. All assessments, including PK sampling, should continue per protocol even if the dose rate is reduced. Time from initiation of study drug infusion to completion must not exceed a total of 48 hours.

Dosing may be discontinued at any time at the discretion of the investigator. Reasons for which the investigator may discontinue the study drug include, but are not limited to, serious or intolerable AEs suspected to be causally related to study drug. In the event that study drug

[redacted]

administration is discontinued, regardless of the reason, the patient will continue to be followed at all study visits defined in the protocol. PK sampling should follow the schedule that is planned for after completion of the study drug (see Section 6.6.2). The exact time and date of study drug discontinuation must be recorded.

Re-administration of study drug, once terminated, is not allowed.

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

[redacted]

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 Concomitant medications/Significant non-drug therapies in the eCRF.

5.5.7 Concomitant treatment

The investigator may prescribe any additional medications and/or supportive care during the study as dictated by the patient's condition, except for those listed in Section 5.5.8 Prohibited Treatment. 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 iv, enteral or topical medications, transfusion of blood products mechanical ventilation, diagnostic examinations, positioning, endotracheal and oropharyngeal suctioning, physio- or ergotherapy, as needed. Any medication or non-medical therapy added, discontinued or modified during the study should be recorded on the eCRF. The investigator should instruct the patient and/or legal guardian to notify the investigator or associated study personnel about any new medications he/she takes after the patient was enrolled into the study.

[redacted]

[redacted] All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded.

[redacted]

5.5.8 Prohibited Treatment

Subjects will not be enrolled in the study if concomitant therapy for AHF includes current or planned treatment with levosimendan or nesiritide during the study. This is because of the potential for the administration of these drugs to interfere with the study endpoints.

Patients on ECMO, VAD or RRT will not be enrolled because of the potential interference of the extracorporeal circuit with the PK profile of serelaxin.

After enrollment, the investigator may prescribe any additional medication as dictated by the patient's 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. Changes to any co-medication or non-medical treatment during the hospitalization should be recorded on the eCRF.

5.5.9 Discontinuation of study treatment

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:

- Withdrawal of informed consent-or assent
- Intolerable adverse events, thought to be related to study drug, which persist
- If the SBP falls <5th percentile for the age of the patient (AHA PALS guidelines 2010, Kleinman 2010, see Appendix 4) and is considered a confirmed SBPDE, then follow the instructions outlined in Section 5.5.5.
- Use of prohibited treatment as per Section 5.5.8
- Pregnancy
- Surgical intervention during the study drug infusion
- A patient should not remain in the ICU/CCU or a continuously monitored step-down Unit for the sole purpose of study drug infusion. The decision to discharge a patient from the ICU/CCU or a continuously monitored step-down unit should be made per SOC. If the serelaxin infusion is still ongoing at the time of transfer out of the ICU/CCU or a continuously monitored step-down unit, the study drug infusion is to be discontinued.

[redacted]

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

Patient withdrawal: Patients/legal guardians may voluntarily withdraw consent or assent for any reason at any time.

Withdrawal of consent or assent occurs only when a patient/legal guardian does not want to participate in the study anymore and, does not want any further visits or assessments and, does not want any further study related contacts and does not allow analysis of already obtained biologic material.

If a patient/legal guardian withdraws consent or assent, the investigator must make every effort to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient/legal guardian or patient are not allowed unless safety findings require communicating or follow-up.

Patients/legal guardians can refuse to participate in specific aspects of the study and/or take study medication at any time without withdrawing consent. Investigators should make every effort to accommodate the needs of the patients to make it possible for them to continue to participate in the remaining aspects of the study.

Lost to follow-up: For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, legal guardians, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until his/her scheduled end of study visit would have occurred.

The investigator must also contact the IRT (Interactive Response Technology) to register the patient's discontinuation from the study drug.

[redacted]

5.5.10 Withdrawal of consent

Patients may voluntarily withdraw consent/assent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a patient does not want to participate in the study anymore and does not want any further visits or assessments and does not want any further study related contacts and does not allow analysis of already obtained biologic material.

If a patient withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information. Investigational study drug treatment must be discontinued and no further assessments conducted. All biological material

[redacted]

that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

5.5.11 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until his/her scheduled end of study visit would have occurred.

5.5.12 Emergency breaking of assigned treatment code

Not applicable

5.5.13 Study completion and post-study treatment

Patient participation will be completed 28 days after the start of the study drug infusion. The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.5.14 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient 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 the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

[redacted] Patients should be seen for all visits on the designated day or time point, or as close to it as possible.

[redacted] If a patient/legal guardian 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 at day 28 and at the end of the 30 days following the last study visit. Documentation of attempts to contact the patient should be recorded in the source documentation.

After identifying a potential patient, an ICF (and Assent, if applicable) must be signed by the parent(s)/legal guardian(s) (and Assent signed by the patient, as applicable) before performing study-related screening procedures that are not considered standard of care for AHF patients

[redacted]

at that site. Procedures that are part of a site's standard of care for an individual with AHF may pre-date the signed ICF. The AE and SAE reporting period will begin at the time the ICF is signed.

Screening will continue until the patient has been deemed eligible for enrollment or screen failed.

[redacted]

Table 6-1 Assessment schedule

[redacted]

[redacted]

[redacted]

[redacted]

6.1 Information to be collected on screening failures

All patients for whom informed consent has been signed but who do not enter the treatment epoch of the study will have the study completion page for the screening epoch completed and will have demographic, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events (AEs) that are not SAEs will be followed by the investigator and collected only in the source data.

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

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex, race, ethnicity, weight and height. Relevant medical history/current medical condition data includes data until the start of study drug. Diagnoses and not symptoms will be recorded on the eCRFs, where possible. 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. Infusion times and rates will be recorded in the eCRF. Study drug and supplies must be made available for inspection by the clinical trial monitor for accountability.

[redacted]

6.4 Efficacy

6.4.1 Hemodynamic assessments

The hemodynamic effects of different doses of serelaxin will be assessed as a secondary endpoint in this study. This will be done at baseline, prior to each dose escalation and at approximately 24 hours after the end of the infusion. Hemodynamic effects will also be assessed for safety at additional time points during the study as outlined in Section 6.5.2. The following hemodynamic measurements will be assessed for efficacy (as available): arterial BP and central venous pressure (CVP), left atrial pressure (LAP), pulmonary artery pressure (PAP – systolic and diastolic), central venous and arterial oxygen saturation, urine output, and blood lactate levels.

[redacted]

6.4.2 Exploratory assessments

[redacted]

[redacted]

6.4.3 Appropriateness of efficacy assessments

[redacted]

6.5 Safety

6.5.1 Physical examination

A complete 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 before every dose escalation as part of the global hemodynamic assessment noted in Section 5.5.4, and is to include the examination of general appearance and vital signs.

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 related to the physical examination made after signing the informed consent, up to and including Day 14, which meet the definition of an AE must be recorded on the Adverse Event section of the eCRF (Section 7.1). Significant findings related to the physical examination 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 completed signed Serious Adverse Event form must be provided to the local Novartis Drug Safety and Epidemiology Department (DS&E) faxed within 24 hours after awareness of the SAE.

6.5.2 Vital signs, respiratory parameters and clinical assessments

Vital signs, respiratory parameters and clinical assessments will be performed at multiple time points as described below. These measurements may be made and recorded by trained healthcare personnel as part of their routine clinical duties, as well as by study personnel.

Vital signs, respiratory parameters and clinical assessments to be evaluated:

- HR, SBP, Mean Arterial Pressure (derived), DBP
- RR (respiratory rate of the patient)
- SpO_2 (pulse oximeter)
- Hourly per kg urine output
- $ETCO_2$ (end-tidal (expiratory) CO_2) or $TcCO_2$ (transcutaneous CO_2), if available
- CVP (central venous pressure) and LAP (left atrial pressure), if available
- PAP (pulmonary artery pressure – systolic and diastolic), if available
- Ventilation parameters (where available – for spontaneously breathing patients only FiO_2 [according to the table in Appendix 7] should be recorded):
    - Mode of ventilation: invasive, non-invasive mechanical ventilation or spontaneous breathing
    - FiO_2 (Oxygen fraction in the inspired gas) [according to the table in Appendix 7] should be recorded in addition to the ventilator parameters (PIP, PEEP, MAP, V_T) specified in Section 6.4.2

[redacted]

- Oxygenation index (FiO2xMAP)/PaO2 (for patients on mechanical ventilation only) and PaO2/FiO2 ratio, will be calculated
- Co-medication and dose (including [dose – per min or hour] or [infusion rate + concentration] for continuous infusions, e.g. inotropes, vasoactive drugs, sedation and analgesia)
- Discontinued co-medications during the interval (all medications)
- Non-medical therapies in the interval (including but not limited to the following: physiotherapy, ergotherapy, endotracheal suctioning or repositioning, mobilization, transportation)

Vital signs, respiratory parameters (including the ventilator parameters PIP, PEEP, MAP, V_T specified in Section 6.4.2) and clinical assessments must be closely monitored during the infusion of the study drug. The time points to be collected in the eCRF for the evaluation of vital signs, respiratory parameters and clinical assessments (hourly time points are approximate) are as follows:

- Baseline
- Every 2 hours for 4 hours at the start of each of the three dose levels
- Every 4 hours for the remainder of each infusion period
- Every 4 hours during the 24 hours post discontinuation or completion of study drug infusion
- Thereafter, every 8 hours until day 5 for as long as the patient is hospitalized. If the patient is discharged prior to day 5, then approximately q24 hr. as an outpatient, up to and including day 5.
- And, anytime there is a clinically significant change in any of the above parameters or an AE/SAE indicative of worsening heart failure (see [redacted] for examples), at any time point during the study. The clinical context should be described by the investigator.

[redacted]

6.5.3 Height and weight

Height/length in centimeters (cm) will be measured at Screening.

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at Screening and Days 1-5, and 14. The basis for the Inclusion Criteria weight (i.e. 2.5 -120 kg) is as follows: pre-operative weight for post-operative patients and weight on hospital admission for non-surgical patients. Body weight during critical care unit stay is to be recorded only if available as per standard of care.

6.5.4 Laboratory evaluations

A combination of central and local laboratories, depending on the type of analysis and the time point, will be used for analysis of all screening, baseline and post-baseline specimens collected according to Table 6-1. [redacted]

For local laboratory results, the laboratory name, test values and the normal ranges relevant to the age of the patient must be entered into the eCRF page. Laboratory values that exceed the boundaries of a notable laboratory abnormality for this patient population should be assessed for AEs and additional evaluations should be performed, as judged appropriate by the investigator. If a laboratory abnormality induces clinical signs and symptoms, or requires therapeutic intervention, this is considered an AE. The diagnosis or medical condition must be entered on the AE screen of the eCRF. If a laboratory abnormality 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. [redacted]

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, MCV, MCH, white blood cell count with differential counts, and platelet count will be measured. Hematology parameters will be analyzed by the Central Lab, if blood volume permits.

6.5.4.2 Clinical chemistry

Blood urea nitrogen (BUN), creatinine, total bilirubin, AST, ALT, alkaline phosphatase, lipase, amylase, lactate dehydrogenase (LDH), sodium, potassium, chloride, calcium, phosphorous, magnesium, bicarbonate, total protein, albumin, uric acid, glucose, cholesterol

[redacted]

and triglycerides will be measured in a central laboratory, if blood volume permits. If not, results from routine testing in the local laboratory will be recorded in the eCRF.

6.5.4.3 Blood gas analysis and lactate

The arterial and central venous samples have to be taken at the same time in order to allow accurate calculation of the arterio-venous oxygen extraction. In patients without arterial line the oxygen saturation from the pulse oximeter should be recorded. [redacted]

6.5.4.4 Urinalysis

Dipstick measurements for specific gravity, protein, glucose and blood will be performed locally.

6.5.5 Electrocardiogram (ECG)

ECGs should be recorded in the supine position, if possible after at least 10 minutes rest to ensure a stable baseline. A standard 12-lead ECG will be performed at screening and at the end of study drug infusion (note: if paper, 3 copies of the same tracing are to be provided). ECGs will be read locally for study entry and diagnostic purposes and will also be read by a Central ECG Reader. The centrally read ECG data will be used for analysis. Each ECG tracing should be labeled with the study and patient number, patient initials (if applicable), date, and kept in the source documents at the study site. Clinically significant abnormalities should be recorded on the relevant section of the Medical History/AE eCRF, as appropriate.

6.5.6 Pregnancy and assessments of fertility

At screening, a locally-analyzed serum pregnancy test will be performed for all females 11 years of age and older and for all females <11 years of age, who are of childbearing potential (menstruation has started). Any patient with a positive pregnancy test at Screening will be excluded from participating in the study. A serum pregnancy test will also be performed locally at the Study Day 14 or the last in-person discontinuation visit for all females 11 years of age and older and for all females <11 years of age, who are of childbearing potential (menstruation has started).

6.5.7 Chest X-ray

A chest X-ray (i.e. standard anterio-posterior view of a thoracic radiograph, in upright position at end-inspiration or end-inflation if possible) should be done within 12 hours of the screening visit. If a study related chest X-ray requires permission by local regulatory authorities and approval has not been obtained, patients may only be included if a SOC chest X-Ray, done within 12 hours of the screening visit, is available. The chest X-ray may be

[redacted]

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. Findings such as pleural (or pericardial – if possible) effusion, lung infiltrates or atelectasis, increased vascular markings, cardio-thoracic index, signs of enlargement of any heart chamber, line, catheter and endotracheal tube placements should be graded (light, moderate, severe – where appropriate) and described in the source document. A radiologist's interpretation is not necessary for the purposes of this study.

6.5.8 Appropriateness of safety measurements

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

6.6 Other assessments

Pharmacokinetic evaluations (serum) will be done for all patients as described in Section 6.2.

6.6.1 Resource utilization

Data regarding healthcare resource utilization will not be collected in this study.

6.6.2 Pharmacokinetics and Immunogenicity

[redacted]

Pharmacokinetic (PK) parameters will include Css (steady state concentration, estimated by C16hr, C32hr and C48hr for each dose level) and CL (clearance, estimated using Css). Additional non-compartmental and compartmental PK analyses may be performed and parameters will be generated based on the suitability of the data.

[redacted]

[redacted]

6.6.3 Pharmacogenetics/pharmacogenomics

Pharmacogenetics will not be performed in this study.

6.6.4 Other biomarkers

[redacted]

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product (see Section 6.5.2 and [redacted] for additional information regarding AEs indicative of worsening heart failure).

The occurrence of adverse events 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, or other assessments.

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

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

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

[redacted]

patients and identifying AEs. Alert ranges for laboratory and other test abnormalities are included in [redacted]

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

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the investigational treatment (yes/no)
- its duration (start and end dates) or, if the event is ongoing, an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE)
- action taken regarding investigational treatment. All AEs should be treated appropriately. Treatment may include one or more of the following:
  - no action taken (i.e., further observation only)
  - investigational treatment permanently discontinued due to this AE
  - concomitant medication given
  - non-drug therapy given
  - patient hospitalized/patient's hospitalization prolonged
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

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

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

7.2 Serious adverse events (SAEs)

7.2.1 Definition of SAEs

An 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

[redacted]

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

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 (see Annex IV, ICH-E2D Guideline).

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

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

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 (see Section 6.5.2 and [redacted] for additional information regarding SAEs indicative of worsening heart failure).

SAEs are monitored continuously and have also special reporting requirements; see Section 7.2.2.

7.2.2 Serious adverse event (SAE) reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 days period should only be reported to Novartis if the Investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be

[redacted]

submitted within 24 hours of the Investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs 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 the study drug, 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 investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the Investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

[redacted]

[redacted]

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.

[redacted]

8 Data review and database management

8.1 Site monitoring

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

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical

[redacted]

information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

[redacted]

8.2 Data collection

[redacted]

8.3 Database management and quality control

[redacted]

[redacted]

8.4 Interim safety and PK data review

As described in Section 3.1, Study design, [redacted], age cohorts will be enrolled sequentially, within each dose group, from age cohort 1 to 4. For each age cohort, 3 patients will be enrolled first into the low-dose group and if it is considered safe after review of all available safety and PK data (up to and including study day 5), then patients will be enrolled into the low-dose group for the succeeding age cohort. No patients will be enrolled into the high-dose group for a given age cohort until data from the low-dose group of that same age cohort and the high-dose group of the preceding age cohort is reviewed and it is considered safe to proceed. Data review is anticipated to include the following, when available:

- AEs and SAEs and their causal relationship to the study drug
- Hypotension events, dose adjustments and discontinuations
- Evidence of pharmacodynamic interactions between serelaxin and co-medications
- Vital signs, respiratory parameters and clinical assessments
- Blood chemistry, hematology, blood gas and serum lactate levels, and renal biomarkers (as available)
- PK

[redacted]

[redacted]

8.5 Adjudication Committee

Not required.

9 Data analysis

9.1 Analysis sets

The following analysis populations will be defined for the statistical analysis:

- Screened set (SCR) – All subjects who signed the informed consent.
- Enrolled set (ES) – All subjects to whom study treatment has been assigned.
- Safety set (SAF) – All subjects in the ES who were exposed to study drug regardless of the exposure duration, and have at least one post-baseline safety assessment. Of note, the statement that a subject had no adverse events also constitutes a safety assessment.
- The PK analysis set (PK) will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and experienced no protocol deviations with relevant impact on PK data.

The number and percentage of subjects in the ES who completed the study and who discontinued the study, and the reason for discontinuation, will be presented for each age cohort and over all subjects, by dose group.

[redacted]

9.2 Patient demographics and other baseline characteristics

Subject demographics (age, age cohort, [redacted] sex, ethnicity, race, weight and height) and baseline characteristics [heart failure history, mode of ventilation (invasive, non-invasive, spontaneous breathing)] will be summarized by age cohort and overall for the ES. Screening [redacted] eGFR will be summarized with standard descriptive statistics. Medical history data will be summarized by age cohort and dose group and for all subjects. Continuous variables will be summarized using n, mean, median, standard deviation, minimum, maximum, and categorical variables will be summarized using frequency and percentage. [redacted]

9.3 Treatments

Overall study drug administration details will be summarized by age cohort and dose group (low-dose group, high-dose group) and for all subjects for the SAF population. This will include study drug administered (yes/no), reason study drug not administered, actual study drug received, and the number of days infused (one or two). 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 by dose group and by age cohort as well as for all patients. In addition, the number of patients whose study medication dose was lowered

[redacted]

or discontinued prematurely, and the reasons for discontinuation, will be summarized by age cohort and dose group and for all subjects.

Concomitant medications and significant non-drug therapies, prior to and after the start date of treatment, respectively, will be summarized by therapeutic class, preferred term, age cohort and dose group for the SAF population.

9.4 Analysis of the primary variable(s)

There are two primary objectives for this study, the assessment of safety and tolerability and the assessment of pharmacokinetics.

The statistical methods for the assessment of safety and tolerability (rate of adverse events, routine assessment of laboratory parameters including those for renal function) are summarized in Section 9.5.2. The statistical methods for the pharmacokinetics variables are discussed in this section.

9.4.1 Variable(s)

Pharmacokinetic parameters will include Css (steady state concentration, estimated by C16hr, C32hr and C48hr for each dose level), and CL (clearance, estimated using the following equation: CL=Rate of infusion/Css). Refer to Section 6.6.2 for time points for pharmacokinetic (PK) assessments.

9.4.2 Statistical model, hypothesis, and method of analysis

The PK parameters Css and CL will be mainly summarized descriptively by age cohort and dose within each dose group. A graphical presentation will be employed to show mean and individual RLX030 concentration-time profiles for each age cohort and each dose group.

[redacted]

The PK parameters Css and CL may be pooled across dose group (high/low-dose) within each age cohort and summarized as appropriate by dose level and age cohort for 10 µg/kg/day and 30 µg/kg/day, respectively.

[redacted]

[redacted]

9.4.3 Handling of missing values/censoring/discontinuations

No imputation will be done for missing values at 16, 32 or 48 hours for the estimation of Css, or at any planned time points for the by-visit summaries. Only values recorded in the data base will be used for the by-visit summaries at these time point.

9.4.4 Supportive analyses

[redacted]

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

Hemodynamic parameters (secondary)

Secondary endpoints will be assessed at baseline, prior to each dose escalation, and at 24 hr post end of infusion. Secondary endpoints will include an assessment of hemodynamic effects on routinely measured hemodynamic parameters as listed below:

- arterial BP
- central venous pressure (CVP)
- left atrial pressure (LAP) and pulmonary artery pressure (PAP– systolic and diastolic), if available
- central venous and arterial oxygen saturation
- urine output
- blood lactate levels

For arterial BP, CVP, LAP, PAP, central venous and arterial oxygen saturation, urine output and blood lactate levels, the absolute values at baseline and each time point (when these parameters are measured), as well as the change from baseline will be descriptively summarized by age cohort and dose group and for all patients.

[redacted]

[redacted]

9.5.2 Safety variables

Adverse events, SAEs and Death

Adverse events (AEs, SAEs and AEs leading to discontinuation) will be summarized by cohort and dose group and for all subjects in the SAF for the entire study period, during each of the 16 hour dose escalation periods and over the post infusion period. Adverse events (number and percent) will be presented by system organ class and MedDRA preferred term.

In addition, a summary of AEs by preferred term and severity, using the worst reported severity grade for each event for the subject, will be provided. The number and percentage of patients with AEs possibly related to study medication will be summarized by age cohort and dose group and for all patients as well. These summaries will be presented for the entire study period, during each of the 16 hour dose escalation periods and over the post infusion period, respectively.

Death (if any) will be summarized by system organ class and MedDRA preferred term as well.

AEs, SAEs and death will be also presented in data listings at individual patient level.

Laboratory, vital signs, body weight and decreased blood pressure events

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

[redacted]

from baseline (mean, confidence interval, median, standard deviation, 1st and 3rd quartiles Q1 and Q3) at each assessment time point by age cohort and dose group and for all subjects. Notably abnormal values for individual subjects will be flagged in data listings.

Vital sign data and clinical assessments (including HR, SBP and DBP, ventilation parameters etc. as described in Section 6.5.2 excluding the efficacy variables specified in Section 6.4.1) will be descriptively summarized as appropriate by presenting absolute values and change from baseline at each assessment time point for each age cohort and dose group and for all patients. In addition, respiratory parameters including FiO_2, and oxygenation index $(FiO_2 xMAP)/PaO_2$ (for patients on mechanical ventilation only), and PaO_2/FiO_2 ratio, will also be summarized by presenting absolute values and change from baseline at each assessment time point by age cohort, dose group and ventilation mode.

The absolute values and change from baseline at each visit in body weight will be summarized descriptively by age cohort and dose group and for all patients.

The number and proportion of patients who experience a confirmed blood pressure decrease event during study drug administration will be provided by dose level within each dose group and age cohort. Further details on confirmed blood pressure decrease events (including whether they result in study drug dose reduction or discontinuation) will be provided as well.

ECG

The ECG findings and central ECG data will be summarized as appropriate by age cohort and dose group and for all subjects in the SAF population.

9.5.3 Resource utilization

Not applicable

9.5.4 Pharmacokinetics

The pharmacokinetics data analysis is described in Section 9.4.

9.5.5 Pharmacogenetics/pharmacogenomics

Not applicable

9.5.6 Biomarkers

[redacted]

9.5.7 PK/PD

[redacted]

[redacted]

9.6 Interim analyses

There will be no interim analysis for this study. However, there will be interim PK and safety data reviews by the PSRC. See Section 3.1 for study design details.

9.7 Sample size calculation

Sample size is guided by feasibility in pediatric patient studies for assessment of safety, tolerability and pharmacokinetics.

The sample size planned for the high-dose group (10/30/100 µg/kg/day) per age cohort will be 6 subjects. With a sample size of 6 subjects per age cohort, receiving RLX030 at various doses, there is ~80% probability to observe an adverse event with an underlying occurrence rate of 24% at least once for each cohort and dose combination during the study. With a sample size of 3 subjects per age cohort, receiving RLX030 at various doses, there is ~56% probability to observe an adverse event with an underlying occurrence rate of 24% at least once for each cohort and dose combination during the study.

Data from 6 subjects will also provide ~80% probability for the 95% confidence intervals (CI) of geometric means of RLX030 Css to fall within the range of (68%U, 146%U), data from 3 subjects will provide ~80% probability for the 95% confidence intervals (CI) of geometric means of RLX030 Css to fall within the range of (39%U, 257%U), where U is the observed geometric mean, assuming a coefficient of variation of 30% [redacted].

[redacted] an additional 3 subjects will be enrolled into a low-dose group (3/10/30 µg/kg/day) in each age cohort. The purpose of this low-dose group is to further enhance the safety by collecting safety data at a starting dose of 3 µg/kg/day up to the adult efficacious dose of 30 µg/kg/day, before enrolling patients in the high-dose group.

These calculations were performed using nQuery.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 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

[redacted]

[redacted]

10.3 Responsibilities of the investigator and IRB/IEC

[redacted]

10.4 Publication of study protocol and results

[redacted]

11 Protocol adherence

[redacted]

[redacted]

11.1 Protocol Amendments

[redacted]

[redacted]

12 References

References are available upon request.

Bani D, Failli P, Bello MG, Thiemermann C, Bani Sacchi T, Bigazzi M, Masini E (1998) Relaxin activates the L-arginine-nitric oxide pathway in vascular smooth muscle cells in culture. Hypertension. 31(6):1240-7

Barry P, Morris K, Ali T (2010) Congestive Heart Failure: Pediatric Intensive Care; Oxford University Press; p. 356-7

Conrad KP (2010) Unveiling the vasodilatory actions and mechanisms of relaxin. Hypertension 56(1):2-9

Conrad KP (2011) Emerging role of relaxin in the maternal adaptations to normal pregnancy: implications for preeclampsia. Semin Nephrol 31(1):15-32

Conrad KP (2011) Maternal vasodilation in pregnancy: the emerging role of relaxin. Am J Physiol Regul Integr Comp Physiol 301(2):R267-75

Conrad KP, Shroff SG (2011) Effects of relaxin on arterial dilation, remodeling, and mechanical properties. Curr Hypertens Rep 13(6):409-20

Danielson LA, Sherwood OD, Conrad KP (1999) Relaxin is a potent renal vasodilator in conscious rats. J Clin Invest. 103(4):525-33

Davidson J, Tong S, Hancock H, Hauck A, da Cruz E, Kaufman J (2012) Prospective validation of the vasoactive inotropic score and correlation to short term outcomes in neonates and infants after cardiothoracic surgery. Intensive Care Med 38:1184-1190

Dschietzig T, Bartsch C, Richter C, Laule M, Baumann G, Stangl K (2003) Relaxin, a pregnancy hormone, is a functional endothelin-1 antagonist: attenuation of endothelin-1-mediated vasoconstriction by stimulation of endothelin type-B receptor expression via ERK-1/2 and nuclear factor-kappaB. Circ Res. 10;92(1):32-40

Du XJ, Bathgate RA, Samuel CS, Dart AM, Summers RJ (2010) Cardiovascular effects of relaxin: from basic science to clinical therapy. Nat Rev Cardiol. 7(1):48-58

Epstein D, Wetzel RC (2006) Cardiovascular Physiology and Shock. Congestive Failure. In: Nichols DG, Ungerleider RM, Spevak PJ, Greeley WJ, Cameron DE, Lappe DG, Wetzel RC (eds.) Critical Heart Disease in Infants and Children. 2nd ed; Mosby Elsevier, p. 42-5

Hogg RJ, Furth S, Lemley KV, Portman R, Schwartz GJ, Coresh J, Balk E, Lau J, Levin A, Kausz AT, Eknoyan G, Levey AS (2003) National Kidney Foundation's Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Chronic Kidney Disease in Children and Adolescents: Evaluation, Classification, and Stratification. Pediatrics 111:1416

Hsu SY, Nakabayashi K, Nishi S, Kumagai J, Kudo M, Sherwood OD, Hsueh AJ (2002) Activation of orphan receptors by the hormone relaxin. Science. 295(5555):671-4

Kantor PF, Mertens LL (2010) Clinical practice: heart failure in children. Part I: clinical evaluation, diagnostic testing, and initial medical management. Eur J Pediatr 169(3):269-79

Kantor PF, Mertens LL (2010) Clinical practice: heart failure in children. Part II: current maintenance therapy and new therapeutic approaches. Eur J Pediatr. 169(4):403-10

[redacted]

Kay JD, Colan SD, Graham TP Jr (2001) Congestive heart failure in pediatric patients. Am Heart J 142(5):923-8

Kim JJ, Rossano JW, Nelson DP, Price JF, Dreyer WJ (2008) Heart Failure in infants and children: Etiology, Pathophysiology, and Diagnosis of heart failure. In: Nichols DG (ed. In chief) Roger's Textbook of Pediatric Intensive Care. 4th ed; p. 1064-74

Kleinman ME, Chameides L, Schexnayder SM, Samson RA, Hazinski MF, Atkins DL, Berg MD, de Caen AR, Fink EL, Freid EB, Hickey RW, Bradley S. Marino BS, Nadkarni VM, Lester T, Proctor LT, Faiqa A, Qureshi FQ, Sartorelli K, Topjian A, van der Jagt EW and Zaritsky AL (2010) Part 14: PALS (Pediatric Advanced Life Support): 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation;122:S876-S908

Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, Lurie PR, McCoy KL, McDonald MA, Messere JE, Colan SD (2003) The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med 348(17):1647-55

Madriago E, Silberbach M (2010) Heart Failure in Infants and Children. Pediatric Review 31:4-12

Massin MM, Astadicko I, Dessy H (2008) Epidemiology of heart failure in a tertiary pediatric center. Clin Cardiol 31(8):388-91

Neumann T, Biermann J, Erbel R, Neumann A, Wasem J, Ertl G, Dietz R (2009) Heart failure: the commonest reason for hospital admission in Germany: medical and economic perspectives. Dtsch Arztebl Int 106(16):269-75

NHLBI (2004) The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents: National High Blood Pressure Program Working Group on High Blood Pressure in Children and Adolescents. Pediatrics 114:555–576

Nugent AW, Daubeney PE, Chondros P, Carlin JB, Cheung M, Wilkinson LC, Davis AM, Kahler SG, Chow CW, Wilkinson JL, Weintraub RG (2003) The epidemiology of childhood cardiomyopathy in Australia. N Engl J Med 348(17):1639-46

Pettersen MD, Du W, Skeens, ME, Humes RA (2008) Regression Equations for Calculation of *Z* Scores of Cardiac Structures in a Large Cohort of Healthy Infants, Children, and Adolescents: An Echocardiographic Study. Journal of the American Society of Echocardiography 21(8):923-934

Ricci Z, Ronco C (2013) Neonatal RIFLE. Nephrology Dialysis Transplantation 0:1–3

Schwartz GJ, Work DF (2009) Measurement and Estimation of GFR in Children and Adolescents. Clin J Am Soc Nephrol 4: 1832–1843

Teerlink JR, Metra M, Felker GM, Ponikowski P, Voors AA, Davison Weatherley B, Marmor A, Katz A, Grzybowski J, Unemori E, Teichman SL, Cotter G (2009) Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): a multicentre, randomised, placebo-controlled, parallel-group, dose-finding phase IIb study. Lancet 373: 1429–39

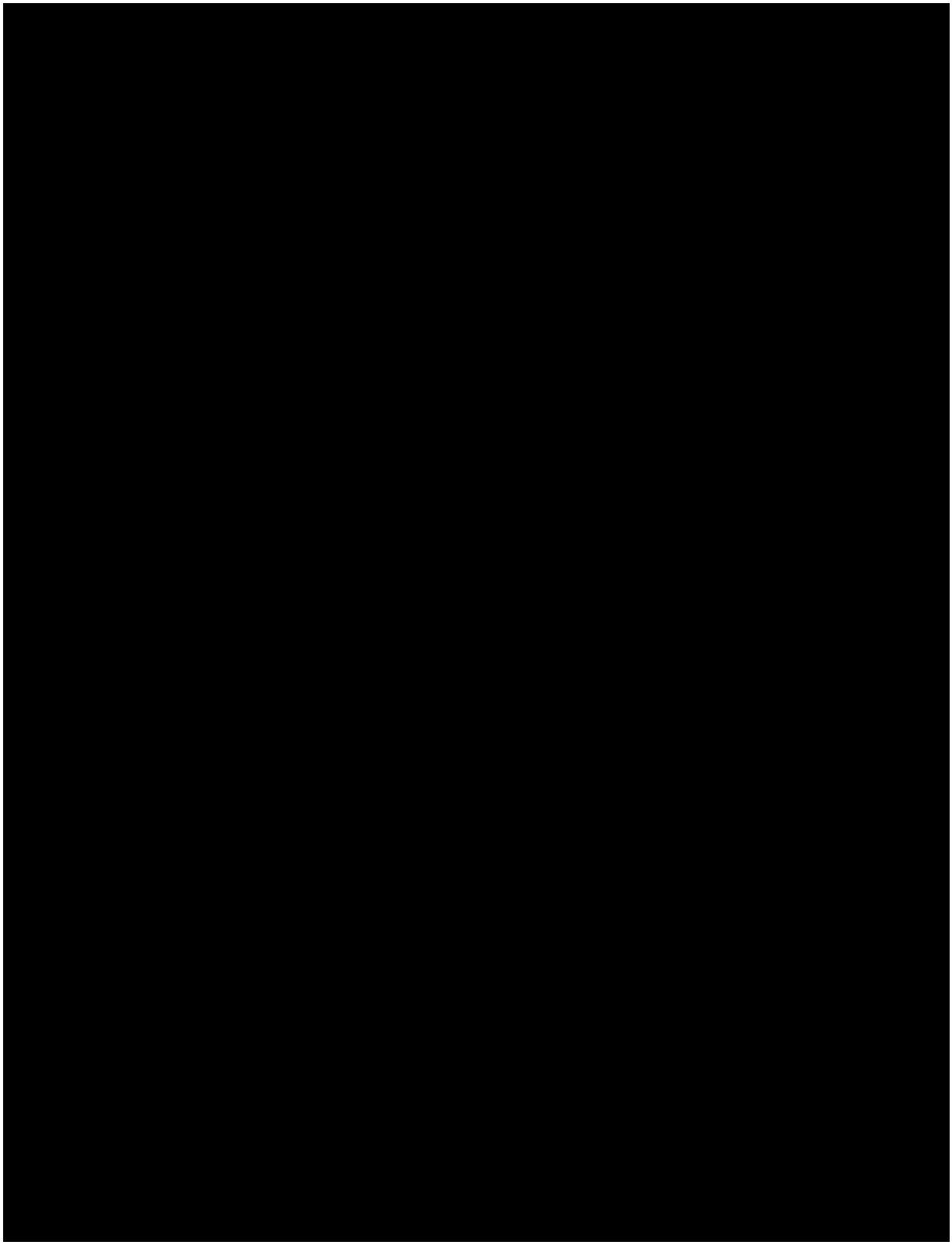
Teerlink JR, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, Ponikowski P, Unemori E, Voors AA, Adams Jr KF, Dorobantu DI, Grinfeld LR, Jondeau G, Marmor A, Masip J, Pang PS, Werdan K, Teichman SL, Trapani A, Bush CA, Saini R, Schumacher C,

[redacted]

Severin TM, Metra M (2013) Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. Lancet 381: 29–39

Tseng CH (2010) Clinical features of heart failure hospitalization in younger and elderly patients in Taiwan. Eur J Clin Invest 41(6):597-604

[redacted]



[redacted]

[redacted]

15 Appendix 3: 25th Percentile Systolic Blood Pressure Table

Table 15-1 25th Percentile Systolic Blood Pressure Table*

		SBP (mmHg)	SBP (mmHg)
Age	BP percentile	Boys, 50th percentile in height	Girls, 50th percentile in height
<1 month	25th estimate**	70	70
<1 year	25th estimate**	75	75
1 year	25th	78	80
2 years	25th	82	81
3 years	25th	84	83
4 years	25th	86	84
5 years	25th	88	86
6 years	25th	89	88
7 years	25th	90	89
8 years	25th	92	91
9 years	25th	93	93
10 years	25th	95	95
11 years	25th	97	97
12 years	25th	99	99
13 years	25th	102	101
14 years	25th	104	102
15 years	25th	107	103
16 years	25th	109	104

[redacted]

17 years	25th	112	105

*Calculated 25th percentile SBP values, based on data provided in the NHLBI (2004): The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents: National High Blood Pressure Program Working Group on High Blood Pressure in Children and Adolescents

** Estimate based on calculated 25th percentile SBP values for 1 yr + and AHA PALS Guidelines for the 5th percentile SBP (Kleinman 2010)

[redacted]

16 Appendix 4: 5th Percentile Systolic Blood Pressure Table

Table 16-1 5th Percentile Systolic Blood Pressure Table (AHA PALS Guidelines)

Age	SBP percentile	SBP (mmHg)
<1 month	5th	60
<1 year	5th	70
1 year	5th	72
2 years	5th	74
3 years	5th	76
4 years	5th	78
5 years	5th	80
6 years	5th	82
7 years	5th	84
8 years	5th	86
9 years	5th	88
10 years	5th	90
11 years	5th	90
12 years	5th	90
13 years	5th	90
14 years	5th	90
15 years	5th	90
16 years	5th	90

[redacted]

17 years	5th	90

* AHA PALS guidelines 2010 (Kleinman 2010) are widely used criteria for hypotension in AHF patients. The formula (for 1 y/o and older: 70 mmHg + 2 x Age, up to age 10) is understood to provide the 5th BP percentile up to 10 y/o. For children >10 y/o, the AHA PALS guidelines 2010 5th percentile is set at 90 mmHg. . NOTE: This formula approximates the population-based 5th percentile BP data; however, the margin of error increases with increasing age, with the PALS formula value generally providing a lower value.

[redacted]

[redacted]

[redacted]

19 Appendix 7: Oxygen delivery devices and FiO_2

Table 19-1 Oxygen delivery devices and FiO_2

Oxygen Device	FiO_2 to be captured	Comment
Nasal Prongs/cannulas	1-2 l/min 25% 3-4 l/min 30% 5-6 l/min 35%	O_2 delivery depends on the flow Indicated FiO_2 is approximate, actual FiO_2 depends on the patients breathing pattern and device positioning
Simple O_2 mask	6-8 l/min 35% 8-10 l/min 45%	O_2 delivery depends on the flow Indicated FiO_2 is approximate, actual FiO_2 depends on the patients breathing pattern and device positioning
Non-rebreathing mask	10-15 l/min 90%	O_2 delivery depends on the flow Indicated FiO_2 is approximate, actual FiO_2 depends on the patients breathing pattern and device positioning
Venturi mask	24 – 50% depending on the connector used	Record what is indicated on the connector
Mask or helmet non-invasive ventilation	21-100%	Record ventilator reading
Invasive ventilation	21-100%	Record ventilator reading

[redacted]

[redacted]

[redacted]

[redacted]