22 May 2014
EMA/303748/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Reasanz

International non-proprietary name: serelaxin

Procedure No. EMEA/H/C/002817

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Product information

Name of the medicinal product:	Reasanz
Applicant:	Novartis Europharm Ltd Wimblehurst Road Horsham West Sussex RH12 5AB UNITED KINGDOM
Active substance:	serelaxin
International Nonproprietary Name/Common Name:	serelaxin
Pharmaco-therapeutic group (ATC Code):	C01DX21
Therapeutic indication (as applied for) :	Reasanz is indicated for the treatment of acute heart failure and to reduce mortality in patients with acute heart failure.
Pharmaceutical form:	Concentrate for solution for infusion
Strengths:	1 mg/ml
Route of administration:	Intravenous use
Packaging:	vial (glass)
Package size:	1 vial

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List of abbreviations

AA	Aldosterone antagonists
ACE	Angiotensin converting enzyme
AE	Adverse event
AHF	Acute Heart Failure
AR	Assessment report
ARB	Angiotensin receptor blocker
Asp	Aspartate, Aspartic acid
AUC	Area under the concentration-time curve
AUC0-t	Area under the serum concentration-time curve from time zero to time t, using the linear trapezoidal rule. Concentrations below the LLOQ are set to zero and therefore excluded from the calculation. Actual sample collection times are used. Where 0-t is shown as τ this denotes the AUC under a dosing interval
AUCinf	Area under the serum concentration-time curve from time zero to infinity. For extrapolation to infinity Clast / λz is used, where Clast is the estimated concentration at the last sample time point above LLOQ from linear regression of the terminal elimination phase
BET	Bacterial endotoxins test
BNP	B-type natriuretic peptide
BP	Blood Pressure
bpm	beats per minute
BUN	Blood urea nitrogen
C48hr	The observed serum concentration at 48 hours after the start of drug administration
CBL	Chesapeake biological laboratories
CBPDE	Confirmed Blood Pressure Decrease Event
CCU	Coronary Care Unit
CEC	Clinical Endpoint Committee
CHF	Chronic Heart Failure
cGMP	Current good manufacturing practice
CI	Cardiac Index
CL	Rate of clearance (serum or systemic)
CL and CL/F	Systemic (or total body) clearance, calculated as Dose / AUCinf following intravenous administration. For extravascular administration where absolute bioavailability is less than 100%, clearance is represented as CL/F
Clast	Last observed serum concentration
CLCR	Creatinine clearance
Cmax	Maximum serum concentration after a single dose
CMO	Contract manufacturing organisation

CNS	Central nervous system
CO	Cardiac output
CPP	Critical process parameter
CRF	Case Report Form
CRL	Charles River Laboratories
Css	Steady-state concentration
CTD	Common technical document
CV	Coefficient of variation
CV	Cardiovascular
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DDI	Drug-drug interactions
DNA	Deoxyribonucleic acid
DO	Dissolved oxygen
DP	Drug product
DRE	Disease-related event
DS	Drug substance
E. coli	*Escherichia coli*
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ERK1/2	Extracellular-signal-regulated kinases
ET	Endothelin
ET-1	Endothelin isoform 1
ETA	Endothelial endothelin type A receptor
ETB	Endothelial endothelin type B receptor
FDA	Food and Drug Administration
GCP	Good clinical practice
GD	Gestational Day
GFR	Glomerular filtration rate
GLP	Good Laboratory Practice
hERG	human Ether-à-go-go-Related Gene
HF	Heart Failure
HR	Hazard ratio
hs-cTnT	High-sensitivity cardiac troponin T
IC50	Inhibitory Concentration 50%
ICH	International conference on harmonisation
ICU	Intensive Care Unit

IGF	Insulin-like growth factor
INN	International non-proprietary name
INSL	Insulin-like
IPC	In-process control
Iso-Asp	Isoaspartate, isoaspartic acid
IU	International units
IV	Intravenous(ly)
JVP	Jugular venous pulse
kDA	kilo Dalton
K-M	Kaplan-Meier
LFT	Liver function test
LGR7	Leucine-rich repeat-containing G-protein-coupled receptor 7
LLOQ	Lower limit of quantification
LO	Low volume light obscuration
LOD	Limit of detection
LoQ	List of questions
LOS	Length of Stay
LVEF	Left ventricular ejection fraction
M	Methionine
MAA	Marketing authorisation application
MAP	Mean arterial pressure
MAPK	Mitogen-activated protein kinases
MCB	Master cell bank
Mfg	Manufacturing
MMPs	Matrix metalloproteinases
MRT	Mean residence time
NA	Not applicable
NAS	New active substance
NCE	New chemical entity
NF	National Formulary
NMR	Nuclear magnetic resonance
NMT	Not more than
NNT	Number needed to treat
NO	Nitric oxide
NOAEL	No Adverse Effect Level
NOEL	No Effect Level
NOS	Nitric oxide synthase
NT-pro-BNP	N-terminal pro-brain natriuretic peptide
NTU	Nephelometric turbidity units
NWP	Normalized water permeability
NYHA	New York Heart Association
O/N	Non-key operational parameter
OMCL	Official medicines control laboratory
OOS	Out of specification

PC	Process control
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamic(s)
Ph. Eur.	European Pharmacopoeia
Ph. Helv.	Pharmacopoeia Helvetica
PK	Pharmacokinetic(s)
PT	Preferred terms
PV	Process validation
PVR	Pulmonary vascular resistance
QC	Quality control
QRD	Quality review of documents
RBC	Red blood cells (erythrocytes)
RBF	Renal blood flow
rDNA	Recombinant DNA
RH	Relative humidity
rhRlx	Recombinant human relaxin-2 (manufactured by single chain process)
rhRlx*	Recombinant human relaxin-2 (manufactured by double chain process)
RLX	Relaxin
RLX030	Serelaxin
RMP	Risk management plan
rpm	Revolutions per minute
RS	Reference standard
RSD	Relative standard deviation
RXFP1	Relaxin/insulin-like family peptide receptor 1
RXFP2	INSL3 receptor, has limited serelaxin binding
SAE	Serious adverse event
SBP	Systolic Blood Pressure
SC	Subcutaneous
sCR	serum creatinine
SCS	Summary of clinical safety
SD	Standard deviation
sMDRD	Simplified modification of diet in renal disease formula
SOC	System organ class
SPC	Summary of product characteristics
SST	System suitability test
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Systemic vascular resistance
T½, λz	Terminal elimination half-life (T½) or rate constant (λz) of the semilogarithmic concentration-time curve Tmax Time to reach the maximum observed serum concentration
tmax	Time to the maximum observed serum concentration
TSE	Transmissible spongiform encephalopathies

URL	Upper reference limit
USP	United States Pharmacopoeia
VAS	Visual Analog Scale
Vc	Volume of distribution in central compartment
VEGF	Vascular endothelial cell growth factor
Vp2	Peripheral volume of distribution
Vss	(Apparent) Volume of distribution at steady state
W	Tryptophan
WCB	Working cell bank
WFI	Water for injection
WHF	Worsening Heart Failure
WRF	Worsening renal function

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Ltd submitted on 24 December 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Reasanz, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

"Reazanz is indicated for the treatment of acute heart failure and to reduce mortality in patients with acute heart failure."

The legal basis for this application refers to:

Article 8(3) of Directive 2001/83/EC - complete and independent application. The applicant indicated that serelaxin was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0288/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001168-PIP01-11-M01 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance serelaxin contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 16 December 2010. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: the United States of America.

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Pieter de Graeff Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 24 December 2012.
- The procedure started on 30 January 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 April 2013 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 April 2013 (Annex 2).
- PRAC RMP Advice and assessment overview adopted by PRAC on 16 May 2013 (Annex 3).
- During the meeting on 30 May 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 31 May 2013 (Annex 4).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 27 August 2013.
- The summary report of the inspection carried out at the following sites: two investigators sites (in Italy and Hungary) and one sponsor site (Novartis USA) between 6 May and 6 August 2013 was issued on 4 September 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 October 2013 (Annex 5).
- During the CHMP meeting on 24 October 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and during oral explanation by the applicant (Annex 6).
- PRAC RMP Advice and assessment overview adopted by PRAC on 05 December 2013 (Annex 7).
- The applicant submitted the written responses to the CHMP List of Outstanding Issues on 22 November 2013.
- During a meeting of a SAG on 9 December 2013, experts were convened to address questions raised by the CHMP (Annex 8).
- Joint Rapporteur/Co-Rapporteur Assessment Report on the responses provided by the applicant, dated 26 November 2013 (Annex 9).
- During the CHMP meeting on 19 December 2013, the outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- Updated Joint Rapporteur/Co Rapporteur Assessment Report on the responses provided by the applicant dated 5 January 2014 (Annex 10).

- During the meeting on 23 January 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Reasanz.

Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Kristina Dunder Co-Rapporteur: Andrea Laslop

- The applicant submitted written notice to the EMA on 28 January 2014 to request a re-examination of Reasanz CHMP opinion of 23 January 2013.
- During its meeting on 20 February 2014 the CHMP appointed Kristina Dunder as Rapporteur and Andrea Laslop as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 27 March 2014 (Appendix 2 of Final Opinion) including the justification for consideration of its application for conditional marketing authorisation. The re-examination procedure started on 28 March 2014.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 22 April 2014 (Annex 11). The Co Rapporteur's Assessment Report was circulated to all CHMP members on 23 April 2014 (Annex 12).
- During a meeting of the Scientific Advisory Group (SAG) CVS on 12 May 2014, experts were convened to consider the grounds for re-examination (Annex 13).
- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 13 May 2014 (Annex 14).
- During the CHMP meeting on 20 May 2014, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 22 May 2014, in the light of the scientific data available and the scientific discussion within the Committee, the CHMP re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the conditional marketing authorisation.

2. Scientific discussion

2.1. Introduction

Heart failure (HF) is a major worldwide health problem and the most frequent cause of admission to hospital in patients older than 65 years (*Roger VL Circulation 2012*). Although existing treatments substantially improve the clinical course and prognosis of ambulatory patients with chronic heart failure (CHF), treatment of patients admitted to hospital for acute heart failure (AHF) has not changed in recent decades (*McMurray, Eur Heart J 2012; Damasceno A, Arch Intern Med 2012; Chen J, JAMA 2011*) with no treatments showing safe improvement in outcomes. Despite a favourable response to initial treatment, most patients remain symptomatic at 24 h and up to 25% develop worsening

symptoms during the hospital stay. Sustained relief of these signs and symptoms remains an important goal of treatment (*Gheorghiade M, JAMA 2007*). Admission to hospital for HF portends an increased risk of poor outcomes, with a 5–15-times increase in the risk of death compared with ambulatory patients and a mortality rate of 10–20% in the 6 months after hospital discharge (*Gheorghiade M, J Am Coll Cardiol 2009; Solomon SD, Circulation 2007*). Although hospital admission could simply herald disease progression, this event and the related interventions might also directly contribute to poor outcomes through increased neurohormonal and inflammatory activation, haemo-dynamic compromise, and consequent end-organ damage.

Relaxin (H2) is a naturally occurring peptide hormone (molecular weight of 5963 Daltons) that has been associated with many of the maternal physiological responses to pregnancy. The investigational product, serelaxin, is produced by recombinant DNA technology in a bacterial expression system and is identical in amino acid sequence and structure to the mature, naturally occurring human relaxin-H2. Relaxin plays a central role in the hemodynamic and reno-vascular adaptative changes: as early as the first trimester of pregnancy, coincident with the rise in circulating endogenous relaxin levels, glomerular filtration rate (GFR) and renal blood flow (RBF) increase, cardiac output and global arterial compliance both rise, and systemic vascular resistance falls. Triggering similar hemodynamic and adaptive changes as seen in pregnancy could potentially be beneficial in the treatment of patients with acute heart failure.

The development of serelaxin was currently focused on the treatment of patients with AHF. The pharmacological effects of relaxin include the production of nitric oxide, inhibition of endothelin-1, inhibition of angiotensin II, production of VEGF, and production of matrix metallo-proteinases. These effects lead to arterial vasodilation, increased arterial compliance, and improved renal hemodynamics.

The proposed indication for serelaxin at the submission of this application was: “Reasanz is indicated for the treatment of acute heart failure and to reduce mortality in patients with acute heart failure.” The dosing recommendation in the proposed SmPC was: “Serelaxin is intended for hospital use only in patients with signs and symptoms of acute heart failure who have dyspnoea at rest or with minimal exertion, normal to elevated blood pressure, and mild to moderate renal insufficiency. It should be used concomitantly with standard of care, including loop diuretics. Systolic blood pressure should be stable and above 125 mmHg prior to administration of serelaxin. Serelaxin has not been studied in patients with systolic blood pressure below 125 mmHg. Reasanz should be administered on the basis of body weight and given via intravenous infusion for 48 hours.”

At day 120 the MAH decided to modify the proposed therapeutic indication to: “Reasanz is indicated for the treatment of acute heart failure and to reduce mortality in adult patients with acute heart failure and normal to elevated blood pressure. Reasanz should be used on top of standard of care, including loop diuretics.” This was proposed to be further modified at day 180 to: “Reasanz is indicated for the symptomatic treatment of acute heart failure in adults with normal to elevated blood pressure. Reasanz should be used on top of standard of care, including loop diuretics”. Finally, following the suggestion from the Scientific Advisory Group experts the proposed indication was further modified to:

“Reasanz is indicated for the symptomatic treatment of acute heart failure in adults with normal to elevated blood pressure systolic blood pressure above 125 mmHg. It should be used on top of standard of care, including loop diuretics.”

2.2. Quality aspects

2.2.1. Introduction

Serelaxin is a recombinant human form of human relaxin-H2, a naturally occurring peptide hormone. Serelaxin is initially synthesized as a pre-pro-peptide, which is a single-chain peptide precursor, composed of 185 amino acids comprising a leader sequence, B-chain, C-peptide and A-chain. The leader sequence is cleaved off to yield pro-relaxin, which shows structural homology to pro-insulin, insulin-like growth factor and nerve growth factor. After removal of the leader sequence and C-peptide, the mature serelaxin molecule is obtained.

2.2.2. Active Substance

Serelaxin is produced by recombinant DNA technology in *Escherichia coli* (*E. Coli*) and it has an identical amino acid sequence and structure to the mature naturally occurring human relaxin-H2 molecule. Serelaxin is a 2-chain heterodimeric molecule, containing a 24-amino acid A-chain and a 29-amino acid B-chain, covalently bound by 2 disulfide bridges. The A-chain has one additional internal disulfide bridge.

The structural elucidation and the physico-chemical and biological characterisation using adequate analytical methods presented in the application have confirmed that the structure and properties of serelaxin active substance have identical features to the mature naturally occurring human peptide hormone relaxin (H2).

Manufacture

Development genetics and cell bank system

Serelaxin is produced in recombinant *E. coli.* using a two-tiered cell banking system of MCB and WCB. The medium used to cultivate and freeze the Manufacturer's MCB and WCBs contained no human or animal derived materials. Procedures followed for the preparation of MCB and WCB were appropriately described. MCB and WCB have been extensively characterized with regards to product identity, genetic consistency and absence of microbial contaminants. Genetic stability at large scale fermentation conditions has been demonstrated by characterization of end of fermentation cultures.

The commercial manufacturing process for serelaxin active substance mainly consists of fermentation, recovery and purification. The manufacturing process is overall well described and sufficiently detailed.

Comparability exercise for Active Substance

The active substance used to manufacture the material used in the phase 3 pivotal trial was manufactured by process 1a. Minor changes were made to the manufacturing process (process 1b). Additional minor changes were made to the downstream process, resulting in process 1c, the validated commercial active substance manufacturing process.

Comparability of active substance obtained from manufacturing process 1a, 1b and 1c (commercial process) has been extensively assessed using three batches from each process. Comparability was demonstrated with release tests, additional side by side characterization, comparison of process performance (impurities) and comparative stability (including degradation behaviour and photostability).

Specification

The active substance specification includes test methods for appearance, pH, identity, quantity, potency, purity, endotoxins and microbial count.

The analytical methods specifically developed for release and stability testing of serelaxin active substance are detailed in the dossier and have been validated in accordance with the principles outlined in ICH Q2 (R1).

The applicant provided an extensive statistical justification of specifications. The presented analytical results demonstrated that serelaxin active substance has the expected primary, secondary and tertiary structures and physical-chemical and biological properties. The biological activity of serelaxin is measured by a cell-based bioassay.

Stability

Based on the data provided the proposed shelf-life for the active substance is considered acceptable.

2.2.3. Finished Medicinal Product

Reasanz finished product is presented as a clear sterile, concentrate for solution for infusion containing the active substance in sodium acetate buffer solution.

The container closure system for Reasanz consists of 6 mL colourless type I glass vials closed with a rubber stopper. The rubber stopper is sealed with a flip-off crimp cap. Vials and stoppers are in compliance with the requirements of the European Pharmacopoeia (Ph. Eur.) Compatibility of the primary packaging materials was evaluated for any potential extractables or leachables and is sufficiently addressed in the dossier.

Pharmaceutical Development

The excipients of the finished product are water for injections as solvent, sodium acetate/sodium acetate trihydrate as buffering agent, and hydrochloric acid and sodium hydroxide for pH adjustment.

Compatibility of serelaxin active substance with excipients has been established during the formulation development, finished product development and stability studies. The excipients used are standard pharmacopoeial excipients. The excipients were chosen taking into account compatibility with serelaxin, stability, solubility and local tolerance.

The information provided on pharmaceutical development is considered satisfactory.

Adventitious agents

TSE compliance and Virus safety

The active substance is manufactured and purified in the absence of human or animal-derived materials. All raw materials used in the production of serelaxin active substance are either of compendial quality or tested according to internal specifications. No raw materials of human or animal

origin have been used in the process. In addition, the medium used to cultivate and freeze the cell banks contained no human or animal-derived materials and therefore presents no concerns with regard to TSE risk.

E. coli cells do not support the replication of mammalian viruses. Therefore, there is no contamination risk from adventitious animal viruses during the production of serelaxin active substance and finished product. The only virus-like agents that can infect *E. coli* are bacteriophages. In order to ensure microbial safety of serelaxin active substance and finished product, the Master Cell Bank (MCB), Working Cell Banks (WCB) and end of fermentation cultures were analyzed for non-host contaminants and bacteriophages. Testing results showed absence of non-host contamination and absence of bacteriophages for MCB, WCB and end of fermentation cultures.

The information provided confirmed the safety of Reasanz regarding adventitious agents.

Manufacture of the product

The manufacturing process consists of formulation/mixing with excipients, sterile filtration and fill-finish into vials.

Adequate critical process parameters (CPPs) and in-process controls (IPCs) are in place for the filtration and filling steps. The omission of CPPs and/or IPCs for formulation/mixing is considered acceptable as the mixing process is extensively validated (both by characterisation and verification) and robustness of the mixing process and the process parameters have been appropriately demonstrated.

Three validation batches were manufactured which comply with the specifications and pre-defined validation limits. Overall the finished product manufacturing process is generally well described and satisfactorily validated.

Comparability Exercise for Finished Medicinal Drug Product

An extensive comparability exercise has been submitted, which included not only (comparative) release and stability testing, but also extended side-by-side characterisation of batches. Finished product comparability of batches manufactured at the commercial site and batches used in pivotal clinical studies is sufficiently demonstrated.

Product specification

The applicant has provided an extensive (statistical) justification of specifications for the finished product. The information is appropriate and valid and overall the tests selected for release and stability testing of the finished product are adequate.

Stability of the product

Stability studies were performed according to the current ICH guidelines. The results generated during the stability studies support the proposed shelf life and storage conditions.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information about the active substance, serelaxin, was of acceptable quality. Sufficient evidence regarding the manufacturing process has been provided. Specification limits and analytical methods are suitable to control the quality of the active substance.

The finished product was well characterised. The manufacturing process has been satisfactorily described and the validation data shows consistent manufacture. The proposed specifications for the finished product were justified based on batch and stability results, and are in general adequate for assuring the product quality and therefore were accepted.

The stability program is in general considered satisfactory. The results generated during the stability studies support the proposed shelf life and storage conditions.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The active substance (serelaxin) and the finished product have been appropriately characterised and in general satisfactory documentation has been provided. The manufacturing process is overall, well described. The IPC tests are described and deemed suitable for controlling and monitoring the manufacturing process. The results indicate that serelaxin as well as the finished product can be reproducibly manufactured.

At the time of the opinion the CHMP has identified and recommended an additional point for further investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

Serelaxin has been investigated for a number of indications. Therefore clinical experience was available before the product was developed for currently applied indication. As a consequence the non-clinical package consists of many studies, some of which are not relevant or not needed for the current indication (short-time exposure following heart failure). In this report those studies that were considered not being relevant for the current indication have not been evaluated and the assessment focussed on those studies needed to support the current Application.

The synthetic and recombinant forms of serelaxin (all processes) are identical in amino acid sequence to each other and to the naturally occurring human hormone (A24B29), except hRlx-2 that has an additional four amino acids on its B-chain (A24B33). Even though hRlx-2 is 4-amino acids longer than the endogenous human H2 relaxin, it contains the complete receptor binding site and is biologically active (Hossain et al 2011) however its kinetic profile it's somewhat different from the naturally occurring hormone. The B33 and B29 forms of relaxin have been shown to have similar potencies in an in vitro rat atrial bioassay (Tan et al 2000) and an ex vivo uterine bioassay (Tan et al 1998). The Applicant considered the data generated using hRlx-2 as supportive information (see the Pharmacology section of this report).

One toxicity study (4 weeks monkey) has been performed with a recent (clinical) batch of serelaxin. All other studies have been performed with earlier batches of serelaxin. According to the Applicant, sufficient non-clinical data has been generated to support the conclusion that the materials used in nonclinical studies of serelaxin were both similar to each other and representative of the clinical material, so that data from these studies can be extrapolated to the commercial recombinant single chain Process 1c material. The process 1c material has not been tested in in vivo non clinical and clinical studies. The CHMP agreed that additional nonclinical *in vivo* studies using Process 1c material would add nothing meaningful to the overall evaluation of safety or PK/PD relationships of serelaxin.

2.3.2. Pharmacology

Serelaxin, also referred to as RLX030, is an E. coli-synthesized protein identical to human relaxin 2.

Relaxin is a naturally occurring peptide/protein with pleiotropic effects within the cardiovascular system. Its most widely recognized role is in mediating vasodilation that is a circulatory adaptation to pregnancy. Relaxin is a general vasodilatator, reducing systemic vascular resistance and increasing cardiac output. This is due to effects on the renal vasculature, yet other vasculature is likely to be involved as well. Relaxin's activity is initiated by binding to its cognate receptor, RXFP1, previously called LGR7, which is present in the renal and systemic vasculature. Nitric oxide and the endothelin type B receptor are believed to act as mediators of relaxin's vasodilatatory effect. Other potential mediators of relaxin's vasodilatatory activity are locally produced matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF).

In addition, relaxin affects the reproductive organs (cervix, pubic symphysis, vagina, uterus, and mammary apparatus), but the precise effects depend on the species. Also the profiles of relaxin levels in the peripheral blood throughout pregnancy differ strikingly among species. While it appears that the species differences mainly concern the role of relaxin in reproduction/pregnancy, also caution should be exercised when interpreting the clinical relevance of the (animal) hemodynamic effects.

The data provided in the pharmacodynamics section is mainly based on publication available in the public domain with almost no studies performed by Applicant. It is agreed that sufficient relevant data is available, and repetition of (animal) studies is not needed (nor ethical). Reasanz was evaluated in single and repeat dose studies of up to 6 months in mice, rats, rabbits, dogs and monkeys using several routes of administration, including intravenous, subcutaneous bolus, topical (intravaginal and intracervical) and intra-gingival administration.

Primary pharmacodynamic studies

The Applicant provided only two original reports covering primary pharmacodynamics, a GLP *in vitro* immunohistochemistry study (study 1280531), and an *in vivo* study on effects of i.v. serelaxin (study RLX030) on cardiac output, total peripheral resistance, and blood pressure in conscious, aged, male spontaneously hypertensive rats (study RD-2012-50361). All other aspects of pharmacology were documented based on published data, considering that the naturally occurring hormone relaxin has a well-known number of biological effects that indicate a role in regulating vascular tone.

The relaxin receptor, RXFP1 (LGR7), is believed to mediate the physiological effects of relaxin (*Hsu et al 2002, Halls et al 2007*). Relaxin binding sites have been detected in blood vessels from humans, as well as in cells and tissues from the human heart (*Hsu et al 2002, Dschietzig et al 2011*). Orthologues of RXFP1 have also been identified in mice and rats as cognate relaxin receptors (*Scott et al 2004*). RXFP2 (LGR8), a receptor closely related to RXFP1, has a binding affinity approximately 10-fold lower

than RXFP1, but is believed to activate a similar, although not identical, signalling pathway (*Halls et al 2009*). RXFP2 receptors are localized in tissues with a distribution pattern similar to that of RXFP1 (*Hsu et al 2002*).

Serelaxin binds with almost equal affinity to either human or rat relaxin receptors, and human relaxin is shown to be highly bioactive *in vivo* in rodents as well as *in vitro* in rodent test systems. *In vitro* data indicate the off-rate of relaxin from its receptor increases at increasing amount of relaxin. This has been suggested as possible cause for the observed U-shaped haemodynamic dose-response curves observed in some non-clinical and clinical studies.

Multiple studies on the effect of relaxin on the haemodynamic parameters have been performed in rats, and effects on blood pressure have been included in several monkey toxicity studies. Overall it appears that relaxin induces a systemic vasodilation that leads to decreased systemic vascular resistance (SVR) and subsequent increase in (heart) stroke volume (SV) which leads to an increase in cardiac output (CO). Effects on haemodynamic parameters in monkeys were less clear. No major effects on blood pressure and heart rate were seen.

Renal effects of serelaxin include marked increases in glomerular filtration rates and increases in renal plasma flow. These effects appear to be rapid, and may persist for several hours following serelaxin treatment. Relaxin has been shown to have an anti-fibrotic effect in rodents. The Applicant appears to suggest that the anti-fibrotic and potential effects on the extracellular matrix of relaxin may support the long term benefit of serelaxin treatment following AHF. However serelaxin did not demonstrate sufficient efficacy in studies where this substance was used to assess its anti-fibrotic activity. Furthermore, based on the level and duration of serelaxin exposure proposed for the current indication significant effect on angiogenesis and or fibrosis is not to be expected.

Secondary pharmacodynamic studies

Angiogenesis

Serelaxin has been shown to stimulate VEGF secretion from certain cell types in vitro including endometrial stromal and epithelial cells (Unemori et al 1999, Palejwala et al 2002) and macrophages (Unemori et al 2000). Serelaxin induces new blood vessel formation in specific sites containing target cells for relaxin, such as the endometrium (Goldsmith and Weiss 2009). Given the effect of relaxin on VEGF secretion, it is not surprising that serelaxin might have an effect on angiogenesis.

Anti-inflammatory effects

Relaxin has been shown to interact with cells of the immune system. Relaxin stimulates leukocyte adhesion and migration (Figueiredo et al 2006) and counteracts activation of human basophils activated by phorbol ester (Bani et al 2002). It also inhibits lipopolysaccharide induced adhesion of neutrophils to coronary endothelial cells (Nistri et al 2003) and promotes migration and activation of monocytes (Figueiredo et al 2006). Although not well understood, an interaction between relaxin and the glucocorticoid receptor has also been reported (Dschietzig et al 2004, Dschietzig et al 2009a).

Antifibrotic efects

Relaxin has been shown to have anti-fibrotic activity in lung, liver, kidney, skin, heart when administered *in vivo* (Bennett 2009). The clinical relevance of these effects noted in rodent is not clear.

Safety pharmacology programme

The cardiovascular safety of serelaxin has been characterized in four dedicated safety pharmacology studies: three *in vitro* in ion channel studies and one *in vivo* in one dedicated telemetry study in cynomolgus monkeys as well as in acute and sub-chronic multiple dose toxicity studies presented in the toxicology section.

No significant effects on ion current were found. In rats effects on blood pressure have been documented, but no clear effects were observed in the monkey. No clinically significant effects on heart rate were observed, while hypotension was noted as an identified risk of serelaxin.

In some monkeys exposed to serelaxin a small and inconsistent effect on body temperature was noted. No such effects were seen in the clinical studies.

Assessment of respiratory- and CNS-related safety pharmacology end-points were not specifically addressed in the nonclinical safety program with serelaxin. This is agreed, considering the nature of the product and the results of the toxicity studies.

Pharmacodynamic drug interactions

The use of serelaxin in combination with other agents has not been evaluated in preclinical models but serelaxin was used in combination with standard of care (nitrates, diuretics, etc) in Phase 2 and 3 clinical trials.

2.3.3. Pharmacokinetics

The intended clinical route is intravenous administration; therefore this assessment of the PK studies focusses on the pharmacokinetics of serelaxin following IV administration. Also studies using SC as route of administration are evaluated. Other routes of administration (vaginal, gingival) are not found relevant for the evaluation of the current application.

Assay methods

Data were obtained with various ELISA methods. In contrast to what is suggested by the Applicant, not all methods used to detect serelaxin in animal species have been validated. In fact the mostly used method (Q8278/SRLX:4) has only been qualified for human use and for a slightly alternative form of serelaxin (+ 4 amino acids). While formally not validated the Applicant has provided sufficient assurance over the performance of the assays used in the non-clinical studies.

Absorption

Following single IV administration, serelaxin was rapidly cleared from the body. The majority of the administered dose (>90%) was cleared within the first 2 to 3 hours post-dose. In general, exposure increased dose-dependently in a dose proportional manner. It appears that there is little or no change in PK following repeated administration. However both in rats and monkeys accumulation was seen following prolonged administration. This increase in exposure coincides with the detection of anti-drug-antibodies (ADA). We therefore agree with the Applicant that the increased exposure was most likely due to the slower clearance of the antibody-bound RLX030 immunocomplexes compared to the clearance of the free unbound serelaxin. In rats exposure in males seems lower than in females, however, no gender differences were apparent in cynomolgus monkey following daily repeated administration. Also in humans no effect of gender on exposure was apparent. The absorption of serelaxin following SC administration was rapid and SC bioavailability was high (67-96%) across the species tested (mice, rats and rabbits). Similar to the PK following IV administration, there was a dose-

proportional increase in exposure following SC administration and there was no apparent impact on kinetics after repeated administration of relaxin (excluding animals which showed an anti-serelaxin antibody response). The effect of (late) pregnancy on pharmacokinetics has intensively been studied. In general, no significant differences were seen in exposure/plasma levels between pregnant and non-pregnant animals. The data also indicate that while foetuses are exposed during pregnancy exposure to serelaxin is likely to be limited (when administered late during pregnancy).

Distribution

Following single i.v. 35S hRlx-2 bolus at GD 19, quantifiable levels of radioactivity were found in all tissues, except pituitary. Levels decreased slowly in all tissues over time, but remained above quantifiable limits in nearly all tissues at 120 hours. The highest levels were seen in the kidneys, liver, serum, total body muscle, and placenta. Lower levels were found in the uterus and total body fat, mammary gland, lung, brain, fetus, spleen, heart and ovary.

In the second study employing 35S rhRlx (89-029-0350-569) quantifiable levels of radioactivity were found in liver, muscle, kidneys, and skin, however after completion of the tissue radioanalyses several weeks later and determination of the material balance for the individual animals, it was shown that the recovery of the 35S for group 1 and 4 was close to 200%.

Metabolism

No studies on metabolism and elimination have been performed which is acceptable for this type of product.

Pharmacokinetic drug interactions

In light of the type of product it is expected that interaction with CYP 450 is very low, and the lack of non-clinical DDI studies are justified.

Pharmacokinetic bridging studies to support manufacturing changes:

- hRlx form versus hRrlx-2 rats: the AUC for hRlx form (17.2+2.6 µg.min/mL) was statistically significant higher (42%) than AUC of hRrlx-2 (10.1+ 1.5), Cl of hRlx (5.9 + 0.9 ml/min/kg) was statistically significant lower (41%) than Cl of Rhlx-2 (10.0 + 1.3 ml/min/kg), and Vss of hRlx (294+37 ml/kg) was statistically significant lower (23%) than Vss of hRlx-2 (380+53 ml/kg).

- rhRlx* form versus hRrlx non pregnant resus monkeys: the AUC, terminal half life, CL, Vc and Vss for rhRlx* were respectively 1.3 lower, 1.9 fold longer, 1.3 fold faster, 1.2 and 2.2 fold larger than for hRlx.

- hRlx-2 form versus hRrlx pregnant and non pregnant resus monkeys. There were significant differences in Cl between hRlx (3-1-3.4 mL/min/kg) and hRlx-2 (6.2-6.5 mL min/kg). The 4 amino acid longer relaxin Cl was almost 2 fold higher the Cl of hRlx, in both pregnant and non pregnant animals.

Overall the non-clinical PK parameter comparison between serelaxin synthetic forms (hRlx and hRlx-2h, 4 aa longer) after i.v. administration in rats and rhesus monkeys (pregnant and non pregnant) showed a statistically significant difference in AUC, Cl and Vss parameters in rats (around 40%), and in Cl in both pregnant and non pregnant animals (around 50%).

Furthermore the PK parameter comparison between serelaxin synthetic and recombinant forms (hRlx and rhRlx* double chain process) after i.v. administration in non pregnant rhesus monkeys showed statistically significant difference in AUC, terminal half life, CL, Vc and Vss (around 26-50%). The ranking order for different serelaxin forms Cl value is hRlx-2 > rhRlx*> hRlx.

Different batches of rhRlx (Recombinant Human Relaxin single chainCBL Lot #1168-1 versus CBL Lot #65802) showed a comparable PK profile.

No PK bridging study is available comparing the two recombinant forms (rhRlx and rhRlx*) after i.v. administration, supportive single s.c. bolus mouse study indicated broadly comparable PK between rhRlx* and rhRlx, but these date are limited to Cmax and half life measurements and they are considered scarcely informative.

Based on the PK bridging studies data supporting the manufacturing changes, the non clinical PK parameter of the different serelaxin synthetic forms used in non clinical programme (hRlx-2, rhRlx*, hRlx) cannot be considered totally equivalent and comparable. However, this issue can be considered overcome in the light of data derived from the 4-week GLP cynomolgus monkey general toxicology study (S630919) which used the newer material (rhRlx-1b) administered i.v, showing a toxicology profile consistent with the previous toxicological studies. Therefore, only this study is considered to be the pivotal study supporting the proposed single use of a 48-hr i.v. infusion of serelaxin in the present clinic application. Moreover, clinical comparability between rhRlx, rhRlx(1a) and rhRlx(1b) and in vitro analytical comparability between all single-chain processes including the proposed commercial process rhRlx(1c) are available.

2.3.4. Toxicology

Single dose toxicity

No treatment related findings were noted in single dose toxicity studies in mice, rats and (cynomolgus and rhesus) monkeys with observation periods up to 14 days.

Repeat dose toxicity

In the rat, following repeated administration, consistent dose-dependent increases in body weight, absolute and/or relative uterine weights, prominence of mammary nipples, and endometrial changes were noted in females. In males and females, slight decreases in serum sodium and chloride relative to vehicle controls were observed. These effects are consistent with the known biological/physiological effect of relaxin. In monkey, no signs of potential safety issues were noted, except for occasional diarrhoea. However this was not observed in the clinical studies, so the clinical relevance of this observation is limited.

Most of the toxicity studies were old using serelaxin batches from previous manufacturing processes. However, one recent toxicity study (4-week IV monkey study, S630919) was performed with a clinical-grade batch. This study is therefore considered pivotal. In this study a dose reduction of the highest dose has been introduced because of on injection site observations possibly due to the daily dosing of relative large volumes with low pH (pH 5). In this study serelaxin induced an inflammation and indurated injection site (highly frequent at high dose, present also in control), accompanied by reversible increase in neutrophil count (2 animals high dose). Diarrhea was present in all dosed with sporadically presence of blood in feces (and urine). Diarrhoea was significantly more pronounced in animals receiving serelaxin compared to controls, thus allowing to hypothesise at least a potentiating serelaxin effect on diarrhoea. In clinical studies with serelaxin, fewer patients treated with serelaxin vs. placebo experienced diarrhoea. (1.9% vs. 3.5%) and constipation (2.3% vs. 2.8%). This indicates that the clinical relevance of the observed diarrhoea in animals is limited.

Macroscopic and microscopic findings were primarily related to vessel injury partially reversible. This effect is probably an exacerbation of the injection site trauma. The NOAEL in this species was considered to be 3 mg/kg/day.

Genotoxicity

No studies on genotoxicity have been performed by the Applicant. This is agreed, considering the nature of the product.

Carcinogenicity

No studies on carcinogenicity have been performed by the Applicant. This is agreed, considering the nature of the product.

Reproduction Toxicity

A relatively large set of reproductive toxicity studies has been performed. Exposures in these studies focused on early pregnancy (including implantation and the early period of organogenesis) and late pregnancy. No adverse effects of treatment were identified on either dams or their offspring. There was no apparent effect on pregnancy maintenance when serelaxin was administered early in pregnancy and no induction of early labour when serelaxin or hRlx-2 was administered late in pregnancy in rhesus monkeys.

2.3.5. Ecotoxicity / environmental risk assessment

According to Directive 2001/83/EC and *Guideline on Environmental Risk Assessment of medicinal products for human use (CHMP/SWP/4447/00)*, medicinal products consisting of substances occurring naturally in the environment, such as electrolytes, vitamins, proteins etc. do not need to be accompanied by an environmental risk assessment, if it can be shown that there is no likely risk to the environment. Hence no Environmental Risk Assessment (ERA) was submitted with this application. This was considered acceptable by the CHMP.

2.3.6. Discussion on non-clinical aspects

Reasanz was evaluated in single and repeat dose studies of up to 6 months in mice, rats, rabbits, dogs and monkeys using several routes of administration, including intravenous, subcutaneous bolus, topical (intravaginal and intracervical) and intra-gingival administration.

Following intravenous administration, the no observed adverse effects level dose in rats was 300 times the human recommended dose and in monkeys was 500 times the human recommended dose.

The data provided in the pharmacodynamics section is mainly based on data available in the public domain with almost no studies performed by the Applicant. The CHMP agreed that sufficient relevant data is available, and repetition of studies in animals is not needed (nor ethical). The vasodilatatory effect of relaxin is well known. The precise haemodynamic responses to serelaxin treatment appear to depend on the study design but also on used strains and species, which hamper the interpretation of the non-clinical studies. In rats, the systemic vasodilation leads to decreased systemic vascular resistance (SVR) and subsequent increase in (heart) stroke volume (SV) which leads to an increase in cardiac output (CO). The effects on haemodynamic parameters in monkeys were less clear, however, no major effects on blood pressure (BP) and heart rate (HR) were seen. The clinical significance of the

serelaxin effects on HR and mean arterial pressure (MAP) observed in rats is unclear since they are not observed in clinical trials. They cannot be defined as rodent specific effects since, although slightly, they are also observed in monkeys.

It was noted by the CHMP that the effect of serelaxin treatment on heart function has not been investigated in an animal model of AHF (animal models with myocardial infarction are available), which may have been the most relevant disease model for the current indication. Despite the fact that the interpretation of the non-clinical studies is hampered by differences in haemodynamic effects between species, and given the current clinical experience, no further non-clinical pharmacology studies are required in the opinion of the CHMP.

2.3.7. Conclusion on the non-clinical aspects

Preclinical studies did not reveal any findings of significance for human use at the recommended dose, based on conventional studies of safety pharmacology and repeated dose toxicity. In a 6-month study in rats, long bone fractures were observed following daily subcutaneous injections at doses representing 3 - 30-fold margins in mg/kg to the human dose. There was no evidence of time dependence or histological correlates. Similar findings have not been observed in 4-week studies in rats or in monkeys. Standard reproductive toxicity studies on fertility, embryofoetal development and peri/postnatal effects have not been performed. However, studies conducted in monkeys covering implantation, early organogenesis and late pregnancy did not show adverse effects of treatment in mothers or offspring. No formal genotoxicity or carcinogenicity studies have been performed with serelaxin. However the non-clinical and clinical data available to date have not indicated any risk for carcinogenicity. The CHMP therefore concluded that the non-clinical development and presented data of serelaxin was satisfactory.

2.4. Clinical aspects

2.4.1. Introduction

The serelaxin clinical development was originally conducted by Corthera, Inc., and clinical study reports have been obtained by the Applicant as part of the acquisition agreement in 2010.

The serelaxin clinical program in the AHF patient population consists of one phase II/III study (RLX.CHF.003 including a phase II Pre-RELAX-AHF and a phase III RELAX-AHF), and one pilot dose escalating (RLX.CHF.001) trial. One additional phase II study (RLX. CHF.002) in decompensated congestive heart failure patients has been prematurely terminated by the Sponsor due to a changed drug development strategy.

In particular, results from the phase II (Pre-RELAX-AHF) and the phase III (RELAX-AHF) studies conducted in subjects with AHF have been submitted to support the MAA of serelaxin in the sought indication.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the Union were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Three of the main and all of the supportive studies are referred to as “legacy” studies since they were conducted by various companies over a considerable time period prior to the acquisition of serelaxin by Novartis. To the best of applicant’s knowledge, all clinical studies were conducted in accordance with regulatory requirements, with the principles of *the Declaration of Helsinki* in effect at the time and following Good Clinical Practice.

A routine GCP inspection was considered necessary for the RELAX-AHF trial before a marketing authorisation could be granted. The outcome of this inspection and the satisfactory responses to its findings are considered an integral part of this procedure. It was considered especially important because:

- the dossier is based on a single pivotal trial,
- a validation issue was suspected in a co-primary endpoint,
- a claim was based on an exploratory endpoint,
- high percentages of patients were affected by ‘significant protocol violations’ including ‘GCP breaches’ that were not further discussed.

The Integrated Inspection Report was circulated on 10 September 2013. The inspection revealed no critical, but 8 major findings. According to the Inspection Report, none of the findings identified were assessed as having any effect in this study on the safety or integrity of the patients or any effect on the quality of data obtained. On the basis of the inspection results it was considered that the data obtained in the clinical trial can be used for evaluation and assessment of the marketing authorisation application. The study Sponsor Corthera Inc has been acquired by the Applicant when approximately 700 patients had been enrolled and about 450 had completed the study. Moreover, site monitoring has been performed by 3 different independent Contract Research Organisations (Covance, PPD and Tango). In general, as result of the set of inspections performed, an adequate oversight of the clinical trial was demonstrated for both periods, before and after Novartis acquisition of Corthera. Based on the observations and findings identified during the inspections and the character of these findings the inspection team is of the opinion, on the basis of the sample inspected, that the clinical trial was performed in compliance with GCP requirements and that the data obtained, documented and reported are reliable.

- Tabular overview of clinical studies

Clinical pharmacology studies

A number of clinical pharmacology studies have been conducted in healthy subjects and in different patient populations, using different routes of administration. In the overview, the applicant addresses only clinical pharmacology data from studies which are relevant for the use of serelaxin as continuous IV infusion in patients with AHF (Table 2.4.1.1).

Table 2.4.1.1 Overview of studies providing clinical pharmacology data.

Sponsor	Study (Number of subjects/patients)	Manufacturing process	Population	Posology	PK and PD measures relevant to clinical pharmacology
Studies in healthy volunteers providing critical PK and/or PD data					
Genentech	[R0006g] (n=25)	rhRlx*	Healthy subjects	Single IV bolus / topical	PK, immunogenicity and safety
Corthera/ Novartis	[CRLX030A2103] (n=40)	rhRlx (1a)	Healthy Japanese and Caucasian subjects	48-hr IV infusion	PK, PD, immunogenicity and safety
Novartis	[CRLX030A2101] (n=49)	rhRlx (1b)	Patients with mild, moderate or severe hepatic impairment matched with healthy controls	24-hr IV infusion	PK, immunogenicity and safety
Studies in patients with heart failure providing PK and/or PD data					
Novartis	[CRLX030A2201] (n=16 for interim PK analysis)	rhRlx (1b)	AHF	20-hr IV infusion	PK
BAS Medical/ Corthera†	[RLX.CHF.001] (n=16)	rhRlx (1a)	CHF	24-hr IV infusion	PK, PD, immunogenicity and safety
Corthera	[Pre-RELAX-AHF] (n=229)	rhRlx (1a)	AHF	48-hr IV infusion	Css and PD
Corthera/ Novartis	[RELAX-AHF] (n=1,161)	rhRlx (1a)	AHF	48-hr IV infusion	Css, immunogenicity and PD
Studies providing supportive PK and/or PD data					
BAS Medical/ Corthera†	[RLX.CR.001]	rhRlx (1a)	Healthy pregnant women at full term	24-hr IV infusion	PK and immunogenicity
Connetics	[R9401]	rhRlx*	Scleroderma	28-day SC infusion	PK, immunogenicity and safety
	[RLXN.C.002 + Extension]	rhRlx (initial process)	Scleroderma	24-48 week SC infusion	PK, immunogenicity and safety
Connetics	[RLXN.C.003]	rhRlx (initial process)	Scleroderma	24-week SC infusion	PK, PD and immunogenicity
	[RLXN.C.004]	rhRlx (initial process)	Scleroderma	24-week SC infusion	PK and immunogenicity
	[RLXN.C.005]	rhRlx (initial process)	Scleroderma	24-week SC infusion	PK, PD and immunogenicity
	[RLXN.C.006]	rhRlx (initial process and 1a)	Scleroderma	24-week SC infusion (not completed)	PK and immunogenicity
	[RLIF.C.001]	rhRlx (initial process and 1a)	Healthy egg donors	14-day SC infusion	PK and immunogenicity
	[RLFM.C.001]	rhRlx (initial process)	Fibromyalgia	8-week SC infusion	PK and immunogenicity
Genentech	[R0187g]	rhRlx*	Healthy subjects	Topical	Immunogenicity
	[R0261g]	rhRlx*	Healthy subjects	Topical	Immunogenicity
	[R0204g]	rhRlx*	Healthy pregnant women at full term	Topical	Immunogenicity
	[R0279g]	rhRlx*	Healthy pregnant women at full term	Topical	Immunogenicity
	[R0282g]	rhRlx*	Healthy pregnant women at full term	Topical	Immunogenicity
BAS Medical/ Corthera†	[RLX.ORTH.001]	rhRlx (1a)	Healthy orthodontic patients	8 weekly intra-gingival injections	PK and immunogenicity

†The company name changed from 'BAS Medical' to 'Corthera' in 2008.

Css, serum concentration at steady state; IV, intravenous; n.a. not applicable; PD, pharmacodynamic(s); PK, pharmacokinetic(s); SC, subcutaneous

Table 2.4.1.2 Completed clinical studies pertaining or relevant to the HF program.

Study Code (Study name, Sponsor#)	Study Design / Objectives	Study Population	Dose Regimen (# subjects)
Completed studies			
RLX.CHF.001 (Pilot Study in CHF) (Corthera)	Phase 1 open label single centre safety and haemodynamic study (PCWP, CO/CI and SVR, serum creatinine, BUN and uric acid).	16 patients with stable congestive heart failure (CHF)	Serelaxin IV infusion, 24-hour, (8-hour intervals) escalating doses 10, 30 100 µg/kg/day (n = 4) 250, 480, 960 µg/kg/day (n=6) 960 µg/kg/day (n=6)
RLX.CHF.003.PRE (Pre-RELAX-AHF) (Corthera)	Phase 2 multicentre, randomised, double-blind, placebo- controlled safety and efficacy study: Dose-finding study evaluated from a number of clinical outcomes, including improvement in dyspnoea, in-hospital outcomes, CV & all-cause mortality)	234 randomised patients hospitalised with AHF, normal to elevated blood pressure, and mild to moderate renal impairment	IV infusion, 48-hour Placebo (n=62) Serelaxin*: 10 µg/kg/day (n=40) 30 µg/kg/day (n=43) 100 µg/kg/day (n=39) 250 µg/kg/day (n=50)
RLX.CHF.003 (RELAX-AHF) (Corthera / Novartis)	Phase 3 multicentre, randomised, double-blind, placebo-controlled safety and efficacy study: Pivotal, Phase 3 study confirming the safety and efficacy observed in Pre-RELAX-AHF	1161 patients hospitalised with AHF, normal to elevated blood pressure, and mild to moderate renal impairment	IV infusion, 48-hour Placebo (n=580) Serelaxin*: 30 µg/kg/day nominal dose rate (n=581)
RLX.CHF.002 (Corthera)	Phase 2 Placebo-controlled, double-blind, multicentre haemodynamic and safety study (Study stopped prior to completion due to a change in corporate strategy)	11 patients with AHF enrolled up to 80 planned; study terminated to initiate RLX.CHF.003	IV infusion, 48-hour Placebo (n=3) Serelaxin: 100 µg/kg/day (n=4) 500 µg/kg/day (n=4)
CRLX030A2103 (Corthera / Novartis)	A Phase 1 exploratory, double-blind, placebo-controlled, parallel group study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenous infusions of	32 Japanese male and female healthy subjects and 8 Caucasian male and female healthy subjects.	IV infusion, 48-hour Placebo (n=8) Serelaxin: 10 µg/kg/day (n=8) 30 µg/kg/day (n=16)

Study Code (Study name, Sponsor#)	Study Design/Objectives	Study Population	Dose Regimen (# subjects)
	Serelaxin at three dose levels in Japanese healthy subjects with an open-label comparison to Caucasian subjects at one dose level		100 µg/kg/day (n=8)
CRLX030A2101 (Novartis)	A Phase 1 single-dose, open-label parallel study to assess the pharmacokinetics of Serelaxin in subjects with mild, moderate and severe hepatic impairment compared to healthy control subjects	25 subjects with mild (n=9), moderate (n=8) and severe hepatic (n=8) impairment 24 matched subjects with normal hepatic function	IV infusion, 24-hour Serelaxin: 30 µg/kg/day (n=49)
CRLX030A2201 (Novartis)	A Phase 2 multicentre, double blind, randomised, parallel group, placebo-controlled study to evaluate the haemodynamic responses to intravenous Serelaxin infusion in subjects with acute heart failure (AHF)	70 subjects hospitalised with AHF	IV infusion, 20-hour Placebo (n=35) Serelaxin: 30 µg/kg/day (n=35)
CRLX030A2202 (Novartis)	A Phase 2 multicentre, randomised, double-blind, parallel group, placebo-controlled study to evaluate the renal haemodynamic effects of Serelaxin at a dose of 30 µg/kg/day or placebo infused for 24 hours in subjects with chronic heart failure (CHF)	88 subjects with CHF, worsening symptoms and mild to moderate renal impairment	IV infusion, 24-hour Placebo (n=44) Serelaxin: 30 µg/kg/day (n=44)

PCWP: Pulmonary capillary wedge pressure, SVR: Systemic vascular resistance, CO: Cardiac output,

2.4.2. Pharmacokinetics

The serelaxin pharmacokinetics (PK) has been characterized through seven clinical pharmacology studies across the dose range from 10 to 960 µg/kg/day i.v.. In addition, further 15 clinical studies provided supportive data for PK, PD or immunogenicity in other patient populations and/or following non IV routes of administration.

Clinical studies in the target HF population provided also PK data, which allowed a sufficient characterisation of the PK in the target population. CL was similar in both healthy subjects and HF patients. Vss was larger in the target population than in healthy subjects, which has been attributed to fluid retention in the HF patients. It is not known whether or not this difference is linked to a difference in the exposure because comparison of exposures between healthy subjects and HF patients was hindered by differences in doses and dosing schedules.

Population pharmacokinetic analysis

The pharmacokinetics of serelaxin could be adequately described in the population pharmacokinetic analysis by a two or a three compartment disposition model depending on the density of PK sampling used in the different studies.

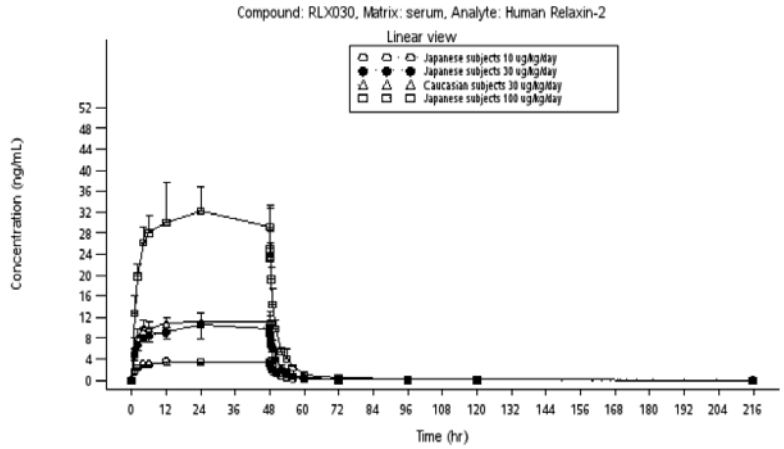
Absorption

Following intravenous infusion, steady-state serum concentrations were reached 12 to 24 hours after the start of infusion. Serelaxin has shown comparable steady-state exposure and systemic clearance following intravenous administration to healthy volunteers or heart failure patients.

Distribution, Elimination, Metabolism

Following IV bolus of 10 µg/kg administration, serelaxin was eliminated rapidly; serum clearance was 168 ± 47 mL/hr/kg, and the mean residence time was 1.6 ± 0.3 hr. The volume of the central compartment and the volume of distribution at steady state were estimated to be 78 ± 39 and 278 ± 95 mL/kg, respectively. The elimination was triphasic with half-lives for the initial, intermediate, and terminal phases of 0.090 ± 0.036, 0.72 ± 0.11, and 4.6 ± 1.2 hr, respectively, with 85% of the area under the serum concentration-versus-time curve due to the first 2 phases. In some studies steady state was considered to be achieved at 8 hours after start of the infusion. However, in other studies with longer infusion periods steady state was reached between 12 and 24 hours (see Figure 2 below). With a molecular weight of 5.96 kDa and a structure identical to the endogenous human peptide, serelaxin is expected to be first filtered via glomerular filtration and then metabolized via either intraluminal metabolism or intracellular lysosomal metabolism in the tubular region of the kidneys. Hence, it is highly unlikely to be detected intact in the urine. No absorption, metabolism or excretion studies have been conducted, considering the biological nature of the molecule and route of administration. In the figure below a typical concentration-time curve of serelaxin after intravenous infusion over a period of 48 hours is given.

Figure 2: Typical concentration-time curve of serelaxin after intravenous infusion



The main elimination pathway of serelaxin is believed to be catabolism by peptidases/proteases across the body including the liver and kidneys. Catabolized fragments of serelaxin are not expected to impact the safety of the patients, as peptide catabolism occurs naturally. Serelaxin is identical in sequence and structure to the endogenously occurring peptide. In women, relaxin is expressed and circulates at low levels in the luteal phase of the menstrual cycle (~50 pg/mL) and is elevated in pregnancy (~1 ng/mL) over a wide range of concentrations (means of 1.2–5.7 ng/mL).

It is not expected that any degradation products of serelaxin are different from those of the endogenous relaxin, due to the comparability of serelaxin with endogenous relaxin.

As serelaxin being a protein will be catabolised to small amino acids that are not active, measurement of these amino acids will not be relevant. Therefore, the lack of data on the pharmacokinetics of these degradation products was considered acceptable by the CHMP.

The pharmacokinetics of serelaxin after subcutaneous and intravenous administration is more or less proportional with the dose administered. Only slight deviation from formal linearity was observed.

Dose proportionality and time dependencies

There was an approximately dose-proportional increase in serelaxin exposure (AUC and Css). Estimates for clearance and Vss were constant across the dose range of 10-960 μg/kg/day.

Special populations

The pharmacokinetics of serelaxin in heart failure patients the mean clearance was 115 mL/hr/kg. Apparent volume of distribution at steady state largely exceeded blood volume (geometric mean = 591 mL/kg), indicating extra-vascular penetration.

Relatively large inter-individual variability was observed for both pharmacokinetic profiles and variables estimates, especially in Vss (CV% were 74% and 116% for arithmetic and geometric means, respectively), at least partially due to the atypical values in 6 out of the 16 (erratic values in the two first samples) subjects who received serelaxin.

In renal impaired patients the clearance of serelaxin is not influenced in a clinical significant way. This was confirmed in the population pharmacokinetic analysis. Also in hepatic impaired patients the pharmacokinetics of serelaxin were not affected.

The population pharmacokinetic analysis showed that gender, race, and age also did not affect the pharmacokinetics of serelaxin in a clinical significant way.

As serelaxin is in all studies dosed on body weight, the influence of weight cannot be estimated adequately and is of no clinical relevance.

Pharmacokinetic interaction studies

As with other endogenous proteins and peptides, there is a lack of a potential mechanism for direct interaction of serelaxin with CYP P450 enzymes (inhibition or induction). Elimination of serelaxin by the liver is expected to be mostly based on receptor-mediated endocytosis and/or nonselective pinocytosis, and then catabolism by proteolysis. CYP P450 enzymes are, therefore, not expected to contribute to the degradation and elimination of serelaxin. Interactions are therefore unlikely to occur and the lack of interaction studies is considered acceptable.

2.4.3. Pharmacodynamics

Mechanism of action

Serelaxin is a recombinant form of the naturally occurring human relaxin-2 peptide hormone. Preclinical studies show that relaxin-2 binds to its cognate G-protein coupled receptor, RXFP1, in the renal and systemic vasculature and in the epithelium of the kidney. Upon receptor binding, relaxin-2 stimulates rapid signalling pathways, leading to activation of nitric oxide synthase as well as sustained signalling pathways with the stimulation of the endothelin type B receptor and expression of angiogenic growth factors and matrix gelatinases. These pathways mediate systemic and renal vascular relaxation along with increased global arterial compliance and cardiac output. The vasoactive properties of relaxin-2 have been substantiated by preclinical or clinical investigations of the maternal circulatory adaptation to pregnancy. The temporal expression of relaxin-2 reaching plasma concentrations of approximately 6 ng/ml in the first trimester is believed to reduce systemic vascular resistance and to increase cardiac output, assuring adequate oxygen transport to the foetoplacental unit.

Primary and Secondary pharmacology

Relaxin is believed to regulate maternal adaptations to pregnancy with several effects potentially relevant to the treatment of AHF.

In animals, relaxin has a broad spectrum of pharmacologic effects. There is a broad variation among species, making extrapolation of data between species or to humans difficult. In humans, important pharmacologic differences may exist between healthy volunteers and HF patients. These differences could (e.g.) be related to neurohormonal activation or exhausted auto-regulation in HF patients. The PD effects of serelaxin that are measured in clinical pharmacology studies are related to its effects on systemic and renal circulation.

In a randomised, controlled study in patients hospitalized with AHF (CRLX030A2201), serelaxin 30 µg/kg/day was administered as a 20-hour IV infusion with the following results:

- Treatment with serelaxin decreased pulmonary capillary wedge pressure (PCWP). The onset of serelaxin's effect was fast (treatment difference at 2 hours: - 2.4 mmHg) and the largest treatment difference in PCWP change from baseline was -3.93 mmHg at 4 hours. The reduction in PCWP change from baseline was sustained after infusion was stopped in the serelaxin group, though no longer statistically significant compared to placebo.
- Serelaxin decreased mean pulmonary artery pressure (PAP). Mean PAP change from baseline was statistically significant at individual time points as early as 30 minutes and up to 21 hours in favour of serelaxin. The peak mean PAP change from baseline over the first 8 hours was (also exactly) -3.93 mmHg.
- No consistent treatment effect was observed in cardiac index (CI).
- Systemic vascular resistance (SVR) and peripheral systolic and diastolic blood pressure (BP) were reduced in serelaxin-treated patients. The effects of serelaxin on SVR occurred within hours from the start of the infusion and were sustained for up to 24 hours after the infusion was stopped.

In an earlier, pilot, open-label study of IV serelaxin spanning a dose range of 10–960 µg/kg/day, no clear dose-response could be established, but dose rates of 10, 30 and 100 µg/kg/day were pharmacologically active. Generally the haemodynamic effects were observed within hours from start of infusion and lasted 4-8 hours following cessation of the infusion. In AHF patients with normal to

elevated BP, the RELAX-AHF (RLX.CHF.003) and Pre-RELAX-AHF (RLX.CHF.003.PRE) studies demonstrated greater decreases in systolic blood pressure (SBP) compared to placebo. Suggesting greater decongestion in patients treated with serelaxin, there was reduction in signs of congestion, e.g., oedema, rales, orthopnoea, jugular venous pressure (JVP) and dyspnoea on exertion. Improved signs and symptoms of congestion may have contributed to the improved liver and cardiac function observed in RELAX-AHF. Serelaxin improved multiple markers of renal function compared to placebo. In the Pre-RELAX-AHF study (RLX.CHF.003.PRE) the pharmacology of serelaxin can be described by a U- or bell-shaped dose-response curve, with the dose response observed in the 30 µg/kg/day group favoured by the Applicant.

In patients with Chronic Heart Failure (CHF) and mild to moderate renal impairment (Study CRLX030A2202), serelaxin 30 µg/kg/day administered as a 24-hour IV infusion increased renal plasma flow (RPF). The treatment difference in average RPF change from baseline was 13-16% (depending on the exact interval) compared to placebo. There was no treatment difference in GFR change from baseline. For filtration fraction, there were treatment differences in change from baseline over of -16% to -22% with smaller increases in the serelaxin group. One site was excluded from the efficacy evaluation in this trial because most (20/21) outliers originated here.

These results in CHF were consistent with an early trial in healthy subjects: increased RPF by 47% from baseline was observed with IV infusion of serelaxin at a dose rate of 0.5 µg/kg/hr over 5 hours, following a bolus of 0.2 µg/kg over 5 minutes (Smith et al 2006). Serelaxin was also modestly natriuretic in this trial.

The human data presented in the Summary of Clinical Pharmacology (SCP) show a clear BP lowering effect. This effect is larger in hypertensive than in normotensive patients. The results from RLX.CHF.001 in HF patients confirm that this BP decrease can be attributed to vasodilatation (decreased SVR). Neither in the RLX030 Population PK Report (based on data from the studies Study CRLX030A2101, Study CRLX030A2103, Pre-RELAX-AHF [Study RLX.CHF.003.PRE] and RELAX-AHF [Study RLX.CHF.003]) nor in RLX.CHF.001 a significant correlation between serelaxin concentrations and CV parameters was found. Based on weight changes as an indirect assessment of possible anti-diuretic effects of serelaxin secondarily leading to haemodilution, no definite conclusions can be made based on current data on whether such an effect exists.

Although BP changes occur within hours, relief of dyspnoea seems more delayed (see e.g. the Likert endpoint in trial RELAX-AHF). Although vasodilatation and lower BP may be involved in dyspnoea relief, other factors seem to play a role. Such factors are not yet elucidated.

Renal blood flow was assessed in the healthy volunteer trial of Smith 2006 and increased by 47% at a serelaxin dose of 12 µg/kg/day. In this same trial, an increase in GFR was absent. These results were confirmed in CRLX030A2202. Creatinine clearance may be increased temporarily during use of serelaxin; it cannot be excluded that this reflects changes in tubular creatinine secretion.

Study RLX.CHF.001 seems to suggest that high doses (e.g. 960 µg/kg/day) of serelaxin are unfavourable with respect to renal function, which is not further explained or understood. In the Pre-RELAX trial, the parameter 'Persistent renal Impairment' showed an adverse trend at the highest dose and mean change from baseline in creatinine showed no clear pattern or dose-response. In the RELAX program, temporary decreases (improvements) of serum creatinine values were observed but these are not supported by urinary data. Thus, no definitive conclusions on renal haemodynamics in HF patients can be drawn.

Serelaxin has an immunogenic potential as is clear from 'legacy' trials, e.g. in systemic sclerosis. The risk of immunogenicity of serelaxin after repeated IV administration cannot be assessed currently due to the lack of data. The risk is addressed in the Risk Management Plan by a proposed randomised controlled trial, the results of which are to be submitted by Q4 2016.

The PD findings that were the basis of the (failed) development of serelaxin in other indications, e.g. the immune-modulatory effect that was possibly beneficial in systemic sclerosis, are not addressed in this dossier. However, the safety of serelaxin as observed in RELAX-AHF (e.g. the absence of findings in AEs) is reassuring.

A concentration-effect relationship has not been established for serelaxin. It is acknowledged that establishing such a relationship may be difficult, because U- or bell-shaped relations may be involved and the concentration with the maximum response may depend on the population (patient, healthy volunteer) and parameter studied.

Only PK, but almost no PD data for genetic differences were provided. Only small numbers of non-Caucasian subjects were included in the trials. As it is known from the experience in ACE inhibitors, race could influence the response to drugs. The currently available data are inconclusive. 'Use in non-Caucasian patients' is included in the RMP as 'missing information'.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Due to the nature of the product (being a small protein, the intravenous route of administration and the only-once dose frequency) the pharmacokinetics (PK) were investigated only to a limited extent. Clearance and volume of distribution were estimated adequately in healthy volunteers. With respect to the population PK analysis, it would have been more useful if for all study data one type of model was developed by the Applicant. In general the models have well described the experimental data, as for the different covariates the visual checks are acceptable. Due to the fact that for the different studies different models were used, no general conclusion can be drawn from the population PK analysis and therefore this analysis will only be used for confirming the influence of co-variables on the PK of serelaxin.

In the study comparing the exposure after administration of the different serelaxin products: rhRlx* and rhRlx, the number of subjects was low and the variability high. Therefore any conclusion from this study should be considered as a rough estimate and not as proof of similarity. The Applicant agreed that there is only limited data available with respect to the comparison of the two forms of serelaxin and stated that the studies with rhRlx* are only supportive studies for this application. The CHMP agreed that there should be no large differences.

In some PK studies steady state was considered to be achieved at 8 hours after start of the infusion. However, this assumption is considered not correct as in other studies it is clear that after 8 hours the concentration of serelaxin in serum did still increase. Taking only the 8 hour serum concentration for calculating the clearance of serelaxin will contribute to a high variability in the estimation of this clinically relevant PK parameter and may lead to discrepancy in the PK parameters between the studies.

The data in renally impaired patients should be interpreted with care as the study design (single time-point PK) and the analytical methods used are sources for uncertainties. However, as these results do

not indicate any evidence for an effect of renal impairment on the PK of serelaxin, no further studies were considered necessary by the CHMP.

Pharmacodynamics

The clinical development program of serelaxin has evaluated the potential use of serelaxin for cervical ripening, pre-eclampsia, infertility, fibromyalgia, orthodontic therapy, systemic sclerosis, and AHF since the late 1980s. However, the development programs of all non-HF indications were terminated due to an insufficient efficacy profile, except for the first study on pre-eclampsia which was stopped for strategical reasons. There is an ongoing Novartis-sponsored clinical trial studying pre-eclampsia.

PD effects of serelaxin in the vasculature are initiated upon binding to its G-protein coupled receptor RXFP1 and trigger the activation of the endothelial endothelin type B receptor (ETB) and nitric oxide (NO) synthase. The NO mediated vasorelaxation results in a reduction of Pulmonary Capillary Wedge Pressure (PCWP), mean Pulmonary Arterial Pressure (PAP) and systemic Blood Pressure (BP). These changes were confirmed in the central haemodynamic study in patients with AHF using a 30 µg/kg/day dose administered as a 20 hours IV infusion [Study CRLX030A2201]. In this trial no change in Cardiac Index (CI) was found. These data support a haemodynamic rationale for the development of serelaxin in AHF.

Serelaxin has been shown to increase Renal Blood Flow (RBF) but not glomerular filtration rate (GFR) in a small open label healthy volunteer study (Smith et al 2006) although only at a low dose (12 µg/kg/day) and after a short infusion lasting for 5 hours. This result was confirmed in study CRLX030A2202, a placebo-controlled study investigating the renal haemodynamic effects of serelaxin at the dose rate of 30 µg/kg/day as iv infusion for 24 hrs compared to placebo in patients with chronic heart failure (CHF).

A clear dose-response relationship for serelaxin is not established with the available PD data. In human data, the exposure-response curve for effects on BP is almost flat. Non-clinical data may indicate a U-shaped or bell -shaped dose-response curve which is potentially the result of negative receptor co-operativity. The results of the human dose-finding trial Pre-RELAX-AHF seem to confirm this U-shaped dose response curve. Therefore, doses higher than 30 µg/kg/day albeit well tolerated may not show greater efficacy.

Anti-drug antibodies have not been observed in studies with IV administration of serelaxin which supports the low immunogenicity potential of the proposed dosing regimen: 48-hour IV infusion. Antibodies have been observed in the studies of longer duration, after at least 2 weeks of dosing with the SC route of administration and in patients with a potentially greater possibility for immune response (scleroderma). The identified antibodies were non-neutralizing yet led to higher serelaxin levels likely by slowing the clearance. However, no toxicity or altered pharmacology was observed in the presence of the antibodies. These findings in scleroderma patients following repeated SC administration are of limited relevance for the proposed dosing regimen (48 hours) and route of administration (IV infusion) in patients with AHF. Proposals for future actions to evaluate immunogenicity of serelaxin after repeated IV administration were included in the proposed RMP and include a randomised clinical trial.

In the past, the relation between PD findings and confirmatory trials has been disappointing in the field of Heart Failure. Therefore, the weight of PD evidence in this dossier is relatively small, but these data – specifically effects on PCWP - support potential efficacy as indicated in the *EMA Guidance on clinical investigations of medicinal products for the treatment of cardiac failure/Addendum on acute heart*

failure (CPMP/EWP/2986/03). The Guideline considers that positive effects on PCWP and symptomatic improvement (dyspnoea) may support a symptomatic indication, provided there are no deleterious effects on mortality. However, the PD results do not provide adequate support for any long-term efficacy of this drug after administration over a short time-frame. The Applicant could have calculated the tissue oxygen delivery based on the CRLX030A2201 data, but such an analysis was not presented. Interpretation of such an analysis may be hampered by baseline differences that occurred in CRLX030A2201 despite randomisation.

2.4.5. Conclusions on clinical pharmacology

Data on pharmacokinetics of serelaxin are limited but in the context of its short-term IV administration the PK is adequately characterised in the opinion of the CHMP. However, discrepancies may be present between the various serelaxin products. Serelaxin is a vasodilatator through the activation of NO-synthase. This may induce changes in SBP, SVR, RAP and PCWP but probably not CO/CI. There is also an effect on renal blood flow but not on GFR. This could be explained by different effects of the medicinal products on venous and arterial systems. Also other effects observed in humans, in particular related to the organ preservation need further elucidation and have not been yet shown conclusively.

2.5. Clinical efficacy

The efficacy of serelaxin in subjects with HF have been studied in PD trials discussed above and in 3 Corthera/Novartis-sponsored trials: (1) RLX.CHF.001, (2) Pre-RELAX-AHF, and (2) RELAX-AHF.

(1) In the Phase 1 RLX.CHF.001 study 16 patients were treated with escalating doses to establish a dose range to be tested.

(2) In the Phase 2, Pre-RELAX-AHF study, a total of 234 subjects with HF were randomised to treatment, and 230 were analysable for safety. This study evaluated 4 doses of serelaxin (approximately 10, 30, 100, and 250 µg/kg/day) vs. placebo and thus provided data to select the optimal IV dose to be taken forward for use in the subsequent Phase 3 RELAX-AHF study.

(3) The Phase 3 RELAX-AHF study enrolled 1161 patients with AHF to treatment, of whom 581 patients were randomised to receive IV serelaxin, and 580 to receive matching placebo (both administrated on top of the current standard-of-care treatment for AHF that included loop diuretics). Serelaxin was administered according to a weight-range adjusted dosing table, based upon the dose with the best benefit/risk assessment from the Pre-RELAX-AHF study.

In the serelaxin AHF program, the Applicant chose the IV route over the SC route to allow a rapid onset of effect, which would be appropriate for acute therapy in AHF patients. This motivation is valid and in addition the IV route may allow dose titration in case of hypotension. In the Pre-RELAX trial, serelaxin was administered using a syringe pump, but in the RELAX trial and in the currently proposed SmPC a 250 ml dextrose infusion was used. This choice seems not further justified. Both options were considered acceptable by the CHMP, but the fluid restriction achieved by using a syringe pump seems preferable in this disease condition.

The interpretation of RLX.CHF.001 with respect to the optimal dose is difficult, because the middle dose group was not comparable to the lower and higher dose groups with respect to some disease characteristics. During the design of (aborted) trial RLX.CHF.002, dose levels of 100 and 500 µg/kg/day were selected, while during the design of Pre-RELAX-AHF lower dose levels of 10-250

µg/kg/day were selected based on the same trial. Based on the data from Pre-RELAX-AHF, the dose range studied in that trial should include the optimal dose for serelaxin in AHF, but further tuning of the dose in the range 10-100 µg/kg/day appears possible.

The Applicant defined a number of categorical weight ranges used to determine dose and fixed infusion volume and speed. The alternative would have been to use a fixed solution with the infusion speed adapted to the patient's weight. The Applicant's proposal was considered acceptable by the CHMP, because there seem to be no data supporting either choice. The variation in doses administered in the RELAX program could possibly be leveraged as an additional dose optimisation effort. This could allow evaluating long-term outcomes (e.g. Day 180 mortality) to be used for dose selection or optimisation.

The mainstay of the development program for serelaxin in AHF were a single Phase II trial (Pre-RELAX-AHF) and a single pivotal Phase III trial (RELAX-AHF).

2.5.1. Dose response study (Pre-RELAX)

Study Pre-RELAX was a Phase II, randomised, double-blind, study with 234 patients receiving a continuous intravenous (IV) infusion for up to 48 hours, of placebo or serelaxin (10, 30, 100 or 250 µg/kg/day) in a randomised ratio of 3:2:2:2:2. Patients in all treatment groups also received standard therapy for AHF.

As the design and the populations studied of the Pre-RELAX and RELAX trials were very similar, comments with respect to these are included in connection to the main study, and omitted here for brevity.

A large number of variables were tested statistically. No correction was done for multiplicity and p values up to 0.20 were considered a 'trend'. As a dose-finding technique, these choices may be acceptable, but the exploratory nature of the findings and the possibility (probability) of chance findings should be clearly kept in mind.

There are some differences between treatment groups in baseline characteristics of the Pre-RELAX mITT population, e.g. median age (70 to 74 years), or NT-proBNP (2791 to 4065 pg/ml). This is inevitable, but stresses again that the results should be interpreted only in an exploratory sense.

Taking this into consideration, the 10, 30 and 100 µg/kg/day dose levels showed promising results with safety comparable to placebo (Table 1).

Table 1 Pre-RELAX-AHF: Serelaxin effects on primary treatment targets by dose (with RELAX results for comparison)

	Placebo	Serelaxin				RELAX	
Dose µg/kg/d		**10**	**30**	**100**	**250**	**Placebo**	**Ser. 30**
N =	61	40	42	37	49	580	581
Proportion of subjects with moderate/marked dyspnoea improvement at 6, 12, and 24 hours (Likert)	23%	27.5% p=0.50	40.5% p=0.037	13.5% p=0.27	22.4% p=0.88	25.9%	26.9% p=0.70
Mean VAS AUC Change from baseline to Day 5 (mm*hour) (95% CI)	1679 (1024-2334)	2500 (1570-3430) p=0.15	2567 (1664-3470) p=0.11	2486 (1531-3441) p=0.16	2155 (1483-2826) p=0.31	2308 (2057-2559)	2756 (2545-2966) p=0.007
Worsening heart failure through Day 5	21%	20% p=0.75	12% p=0.29	14% p=0.40	10% p=0.15	12%	6% P<0.001
Length of hospital stay (days) (95% CI)	12.0 (10.1-13.9)	10.9 (8.1-13.6) p=0.36	10.2 (8.3-12.1) p=0.18	11.1 (8.9-13.3) p=0.75	10.6 (8.7-12.4) p=0.20	10.5 (9.7-11.3)	9.6 (8.9-10.4) p=0.039
Persistent renal Impairment (Creatinine increase of 0.3 mg/dL or more at day 5 AND 14)	7%	8% p=0.87	7% p=0.90	11% p=0.47	15% p=0.19	14%	14% 0=0.92

	Placebo	Serelaxin				RELAX	
Dose µg/kg/d		**10**	**30**	**100**	**250**	**Placebo**	**Ser. 30**
Days alive and out of hospital through Day 60 (95% CI)	44.2 (40.6-47.8)	47.0 (42.9-51.2) p=0.40	47.9 (44.7-51.0) p=0.16	48.0 (44.6-51.3) p=0.40	47.6 (44.1-51.0) p= 0.048	47.7	48.3 p=0.37
CV death or HF/RF re-hospitalisation through Day 60 (K-M estimate %) Cox proportional HR (95% Wald CI)	17.2	10.1 0.55 (0.17-1.77) p=0.32	2.6 0.13 (0.02-1.03) p=0.053	8.4 0.46 (0.13-1.66) p=0.23	6.2 0.32 (0.09-1.17) p=0.085	12.9	13.1 1.02 (0.74–1.41) P=0.895
CV mortality to Day 60 (K-M estimate %) …to Day 180 (K-M estimate %) Cox proportional hazard ratio (95% Wald CI) Fisher's exact test	6.9 14.3	2.5 2.5 0.19 (0.02-1.57) p=0.14	0.0 0.0 0.00 NA p=0.04	2.9 2.9 0.22 (0.03-1.76) p=0.15	6.2 6.2 0.49 (0.13-1.90) p=0.51	4.7 9.6	3.3 6.1 0.63 (0.41-0.96) 0.028

Data shown in shaded boxes are those that were statistically significant vs. placebo or trends (p<0.2). HF/RF: heart failure or renal failure; HR: hazard ratio
Source: [SCE-Table 2-1]

Relief of dyspnoea by Likert scale was assessed as the primary outcome measure. The proportion of subjects with a marked or moderate improvement in subject-reported dyspnoea score using the Likert 7-point scale at both 12 and 24 hours in the absence of WHF symptoms was 40.0%, 50.0%, 24.3%, and 40.8% in the 10, 30, 100, and 250 µg/kg/day groups respectively compared to 44.3% in the placebo group. The mean change in dyspnoea (VAS AUC, another endpoint) at 24 hours was 326.6, 319.2, 277.2, and 278.0 mm*hour in the 10, 30, 100, and 250 µg/kg/day groups respectively compared to 262.4 mm*hour in the placebo group.

The trial failed to identify a dose-response relationship. Higher doses were not consistently more effective. The Applicant describes this as a U-shaped curve, but the optimum of the curve may depend on the parameter studied.

2.5.2. Main study (RELAX-AHF)

Study RELAX-AHF (RLX.CHF.003) was a Phase III, randomised, double-blind study with patients receiving a continuous intravenous (IV) infusion for up to 48 hours, of placebo or serelaxin (nominally 30 µg/kg/day) in a randomised ratio of 1:1. Patients in both treatment groups also received standard therapy for AHF.

Methods

Study Participants

Patients were selected based on a clinical diagnosis of heart failure (supported by X-Ray and laboratory investigations) and the need for intravenous diuretic therapy. As serelaxin decreases BP, selection of patients that were not hypotensive (SBP ≥ 125 mmHg) was appropriate. There was no central adjudication of X-Rays. Inclusion required an estimated glomerular filtration rate between 30 and 75 mL/min/1.73m². Exclusion criteria concerned (among others) recent neurologic events, recent acute coronary syndrome, and hepatic impairment.

In general it seems that the definition of the population includes no effective measure of severity besides 'need for hospitalisation', which is highly subjective, and 'need for IV diuretics', which may be chosen for practical reasons besides medical need. Hypotensive patients or patients in need of intravenous circulatory support were excluded. The burden of an informed consent procedure may also have excluded some severely ill patients, but these may have improved during the 16 hours that were allowed for randomisation. Although dyspnoea at rest or with minimal exertion was required for inclusion, 38% of the included subjects were in NYHA class I-II. The ejection fraction (EF) was >40% in 45% of patients.

Moreover, it is not clear whether the selected patients were really 'acute', as this was only defined by the 'intravenous diuretic' requirement. Not all patients were treated in the ICU or CCU. Also, 16 hours could pass between presentation and randomisation, which is a long time in acute medicine.

The entry criteria of RELAX-AHF are reflected in the proposed SmPC; important groups of patients that were not studied are mentioned in Section 4.4, e.g. subjects with severe renal impairment.

Treatments

The study drug serelaxin was provided as a 1 mg/mL clear, colourless solution in 5 mL vials (3.5 mL fill). Matching placebo was provided in identical vials. Based upon a weight based dosing chart, a specified volume of serelaxin solution was withdrawn from the vials using aseptic technique, and injected into a 250 mL IV bag of 5% dextrose solution in water, according to instructions in the Pharmacy Manual. For brevity, the nominal dose rate of serelaxin in RELAX-AHF is referred to as 30 µg/kg/day. Batch numbers were 2008-101 for Serelaxin 1 mg/mL (in 20mM sodium acetate) and 2083-103 for matching placebo (20mM sodium acetate). The IV infusion was administered for 48 hours (IV infusion).

Outcomes/endpoints

Primary endpoints:

1. Sustained relief of dyspnoea, measured by VAS (5 days).
2. Short term improvement in dyspnoea, measured using the Likert Scale.

Criteria for efficacy:

1. AUC representing the change in patient-reported dyspnoea from baseline measured by 100-mm VAS through Day 5
2. Moderately or markedly better dyspnoea relative to the start of study drug on the 7-point Likert scale at 6, 12 and 24 hours (required at all 3 time-points)

Criteria for positive study:

Based on criteria pre-specified in the study protocol and statistical analysis plan, the study was to have met the primary study objective of demonstrating efficacy of serelaxin in dyspnoea relief if either primary endpoint was statistically significant at the two-sided 0.025 level, or if both tests were significant at the two-sided 0.05 level. (Hochberg procedure)

Secondary endpoints:

1. Days alive and out of hospital through Day 60
2. CV death or re-hospitalisation due to HF or renal failure through Day 60.

Additional endpoints

In the final amended version of the protocol (amendment 5), 18 additional endpoints were specified. Some of these endpoints were assessed at multiple time-points or were composites of 2 or more components.

Biomarkers

Three biomarkers were pre-defined and measured at baseline and at various time points during the follow-up period.

1. Cardiac troponin T, measured with a high sensitivity assay (high-sensitivity cardiac troponin T, hs-cTnT) was an indicator of myocardial damage;
2. NT-pro-BNP was an indicator of the degree of congestion and
3. cystatin-C was an indicator of kidney injury.

Although all-cause mortality at 30 days is the preferred endpoint in the *EMA Guidance on clinical investigations of medicinal products for the treatment of cardiac failure/Addendum on acute heart failure (CPMP/EWP/2986/03)*, dyspnoea as assessed by VAS or Likert scale was considered acceptable. This was also concluded in the EMA/CHMP scientific advice (2010), with the addition that additional efficacy and safety data would be required for authorisation.

Although both the Likert scale and the VAS assess dyspnoea, according to the Applicant they are used complementarily and measure different entities: early and sustained relief. In the scientific advice (SA), the CHMP considered that the primary endpoint should also include persistent improvement in clinical signs of congestion and evidence of short-term safety. However, congestion was captured in exploratory endpoints only, without further justification.

The CHMP SA suggested two alternatives for the Hochberg approach as proposed by the company: Choosing the Likert scale as single primary endpoint would be more in line with the EMA guideline, which requires benefit between 6 and 24 hours to be shown if dyspnoea is chosen as the primary endpoint. Alternatively, a positive trial could be defined to require a positive outcome on both Likert and VAS scales. The company decided to maintain the originally proposed Hochberg approach, without further justification. However, it seems that persistent improvement in dyspnoea (during the hospital stay) could serve as a primary endpoint if supported by improvement in clinical signs of congestion according to the recently published concept for revision of the current guideline. These physician-assessed clinical signs of congestion were captured in RELAX-AHF as additional endpoints.

Data on length of hospitalisation and CCU stay, re-hospitalisations and mortality (both all-cause and cardio-vascular) are captured in the secondary and additional endpoints. These endpoints are suggested in the guideline and thus indeed relevant. The 60-day observation period for the secondary endpoints is appropriate in this disease as any potential additional beneficial effects of serelaxin may take longer than the 30-days period advised by the guideline to become evident.

As a large number of additional endpoints was included, and no correction was done for multiplicity, these endpoints can only be interpreted in an exploratory sense and should be used for hypothesis generation only. Claims based on these exploratory endpoints are not acceptable.

Adjudication of deaths occurring between 60 and 180 days after randomisation was added to the evaluations at a later stage. The results of this additional adjudication only impact an exploratory endpoint and the results strongly resemble the investigator assessment of cause of death. Therefore this additional adjudication can be accepted. Of note, hospitalisations between 60 and 180 days after randomisation were not captured.

Sample size

Power for the primary and secondary efficacy endpoints was estimated using simulations. In the clinical overview, the sample size is described as adequate to detect a treatment effect size of 28% increase in the VAS AUC score; in the CSR, the sample size is described as adequate to detect a minimum clinically meaningful treatment difference of 468 mm-hour (4 mm difference at individual time-points on average) in the VAS-AUC endpoint. The clinical relevance of this definition is not well justified and is also difficult to imagine. An effect size of 15 to 20% of the placebo response was considered clinically relevant by the RELAX-AHF executive committee. (The values finally obtained were 447.7 mm-hour for improved AUC over placebo, 3.8 mm on average higher than placebo, or 19.4% increase).

The original sample size calculation, as described in Amendment 2, mentioned a 92% power to detect a mean 6 mm increase at 2-sided p=0.025 or 80% power to detect a mean 7 mm increase at 2-sided p=0.000625

Randomisation

Patient numbers were assigned sequentially at each study site through the IVRS. The patients were assigned a blinded study drug kit through the IVRS based on the randomisation plan. Each site was assigned a block of the randomisation scheme upon activation; up to one additional block could be assigned automatically by the IVRS using a predefined algorithm based on enrolment. Each study drug kit was labelled with a unique kit identification number and contained 1 vial of serelaxin or placebo. The two types of vials (serelaxin and placebo), as well as the kits, were indistinguishable. The site personnel were instructed to access the IVRS to request assignment of study drug kits for each 24 hour period of dosing. Once the IVRS had been accessed, the caller was asked a series of questions, including whether the weight of the subject was ≥115 kg. If the response was no, a single study drug kit was assigned for each 24-hour dosing period; if the response was yes, 2 kits were assigned for each 24-hour dosing period. For each 24-hour infusion period, study drug was withdrawn from the vial(s) contained in the blinded kit(s) and injected into a 250 mL IV bag of 5% dextrose solution in water according to instructions in the Pharmacy Manual.

Blinding (masking)

The clinical database was locked twice. The first database lock occurred when all patients completed the 60 day evaluation period of the study and all data had been monitored, all data queries were resolved. All follow-up between Day 60 and Day 180 available at that 1st database lock, including Day 180 and interim contacts, were included in the Day 60 database. All planned analyses summarising results by treatment group were performed after the last patient had completed the 60 day evaluation period of the study. For this analysis, group summaries were presented. Individual patient treatment assignments (e.g., listings) were not provided prior to the Day 180 lock. Only members of the data analysis team had access to patient level data and these personnel had no direct role in study operations. These results were shared with a limited group of people the identities of whom have been documented by the Sponsor.

All personnel involved in the operations of the study or with any potential site contact, such as medical monitors, remained blinded to treatment assignments from the time of randomisation until the Day 180 database lock according to the Corthera Unblinding Plan, using the following methods: (1) Randomisation data were kept strictly confidential until the time of unblinding at

Day 180, and were not accessible by anyone else involved in the study with the exceptions noted below. The identity of the treatments was concealed by the use of indistinguishable vials and labels (for vials and for kits).

In the event of a medical emergency, the investigator was to contact the medical monitor to discuss the need to unblind the patient's treatment assignment. Several medical monitors were identified so that one would be available at all times. The treatment assignments were to be made accessible to the investigator should a patient need to be unblinded in an emergency. If it was determined that unblinding was required, the medical monitor would drop off the line and the investigator would be unblinded via the IVRS. Almac recorded all such interactions that occurred via the helpline.

The statistical centre reporting to the DSMB was also unblinded to individual treatment assignments. The centre provided monthly unblinded reports of safety and protocol compliance to the chairman of the DSMB and a report to all of the members of the Board for interim safety meetings, according to the DSMB charter.

Statistical methods

Analysis sets

Statistical analyses were conducted for the primary efficacy outcomes with the ITT set, FAS, and PPS-1 and -2. Efficacy outcomes for the ITT set constituted the main outcomes for this study. The analysis sets used are appropriate.

Primary endpoints

The AUC representing the change from baseline in dyspnoea VAS score through Day 5 (VAS AUC) was compared using a two-sided two-sample t-test as the primary method of analysis. Additional analyses were performed to assess the underlying assumptions of the statistical analysis method. If results suggested noteworthy departures from the assumptions underlying the t-test, supportive analyses such as the Wilcoxon rank sum test or a randomisation-based determination of the p-value for the t-test were to be conducted.

Unless otherwise specified, treatment comparisons for continuous outcomes were made using two-sided two-sample t-tests assuming pooled variances. If the distribution of the responses was markedly non-normal (e.g., highly skewed or contains outliers) then results of the Wilcoxon rank sum tests were reported as well. Tests for the normal distribution of results were conducted by treatment using the Shapiro-Wilk test. Because the Shapiro-Wilk test tends to be overly sensitive to departures from normality in large samples sizes, a more restrictive alpha level was used as the critical value for claiming non-normality ($p \leq 0.005$). Equality of variances was assessed using an F statistic. If the variances were unequal ($p \leq 0.005$) then the results of the t-test using the Satterthwaite method were to be presented in addition to results using the method for pooled variances.

The proportion of patients with moderately or markedly better dyspnoea on the Likert scale at 6, 12, and 24 hours (all three time points) was compared between treatment groups using a chi-square test. The odds ratio and 95% confidence interval (95% CI) were presented.

To control the type 1 error, for the two co-primary endpoints the Hochberg method was used and the secondary endpoints were tested hierarchically. Statistically, this approach preserves the type I error at 0.05. However, as was written in the EMA scientific advice, using two potentially correlated co-primary endpoints and considering the trial to be positive if either endpoint is positive, is questioned. It would mean the trial is positive provided the treatment is beneficial in either one of these aspects - it is also not necessary for it to be shown to be effective in both, nor is it specified that any particular one of them must be positive.

The pre-specified α-level is usually not suitable for an application based on a single pivotal trial.

Imputations

Scores for all VAS and Likert assessments following death or the onset of WHF (either during the index hospitalisation or re-hospitalisation due to HF) were imputed as the worst score observed in any patient at any time point and were carried forward for all time points after the time of onset of the event, regardless of whether the actual score was missing or not.

The rationale for the data imputation in the presence of WHF is that WHF is defined as the patient deteriorating to the point of requiring 'rescue' therapy with pharmacological or mechanical intervention. Thus, symptom scores reported by the subject following WHF no longer represent the effect of the study drug but the effect of the rescue therapy. The imputation assumes that patients with WHF have experienced the worst response; therefore, the worst value observed in the population is imputed from that point forward.

For post-baseline values otherwise missing, a missing score was imputed using linear interpolation between the last preceding and first following non-missing value; if no following non-missing value was available, the last available preceding value was carried forward.

Scores for VAS and Likert assessments following death or the onset of WHF were imputed as the worst score observed in any patient at any time point, regardless of whether the actual score was missing or not. This approach was seriously questioned by the CHMP, formed the basis for major objection during the procedure and the grounds for refusal of this application.

Sensitivity analysis

A sensitivity analysis of the VAS AUC endpoint using the FAS was conducted to examine the effect of data handling conventions on the results. For this analysis, scores for all assessments following a death were imputed as the worst observed value in the analysis population while the baseline observations were imputed for patients with WHF from the time of WHF through to the end of the evaluation period.

More sensitivity analyses were provided in the Day 121 responses, for example an analysis using observed values.

Secondary endpoints

Days alive and out of hospital were compared using the Wilcoxon rank sum test as the primary analysis method. In addition, the median of differences and corresponding 95% CI were presented using the Hodges-Lehmann estimator of shift.

The days from the baseline date to the date of the first event (death due to cardiovascular cause, or re-hospitalisation due to HF or RF, CEC classified) were used for analysis. Patients who died

from a non-cardiovascular cause before Day 60 without an event were censored at the time of death; patients otherwise without an event were censored at the earlier of the last contact date or Day 60. Kaplan-Meier estimates of the rates of the composite event and its components were presented, and treatment groups were compared using a log rank test. Kaplan-Meier plots were presented. Hazard ratios and 95% CIs were estimated from a Cox proportional hazard regression model with treatment as a factor.

Additional (exploratory) efficacy endpoints

Time to event variables were analysed presenting Kaplan-Meier estimates and testing with the log rank test. Change from baseline variables were analysed using t-tests. Variables representing the number of days or multi-categorical variables were analysed using the Wilcoxon rank-sum test. The categorical variables were analysed using chi-squared tests.

Due to the large number of these exploratory variables, and the lack of type-I error-control, chance findings would be expected.

Interim analysis

Four interim examinations of key safety data were planned for the purpose of reporting to the DSMB. All analyses related to the DSMB were carried out by an independent statistical group.

At each interim examination, the DSMB assessed safety and protocol compliance, but could request summaries of the efficacy data to provide an overall assessment of risk versus benefit. For each review of the primary outcomes, an alpha of 0.00001 was considered to have been spent, and the significance level for the final analysis adjusted accordingly. In the responses to the CHMP Day 120 List of Questions, the applicant shows that the adjustment of p-values leads to a very small adaptation, easily hidden after rounding.

Apart from these comments, the statistical methods used are adequately described and are standard and, in general, are considered acceptable.

Results

Participant flow

A total of 1161 patients were randomised to the study. A total of 1035 patients (89.1%) completed the study. The remaining 126 patients (10.9%) who did not complete Day 180 had an interim contact at the time of this data analysis (122 patients, 10.5%), died (106 patients, 9.1%) withdrew consent from follow-up (18 patients, 1.6%), or were lost to follow-up (2 patients 0.2%). A higher proportion of patients in the placebo group died compared to the serelaxin group (11.2% vs. 7.1%). The proportions of patients, who either completed the study, withdrew consent or were still followed, were similar for the serelaxin and placebo treatment groups. The vital status could not be ascertained in 14 patients (12 patients withdrew from follow-up and 2 were lost to follow-up; 1.2%).

Randomisation and treatment all occurred within 72 hours during a single disease episode; as could be expected most subjects who were randomised were also treated. Vital status at Day 180 was not available for 14 (1.2%) patients only, indicating adequate follow-up
Table **2**).

Table 2 Study Pre-RELAX-AHF and RELAX-AHF patient disposition – n (%) of patients (ITT analysis set)

	RELAX-AHF		Pre-RELAX-AHF	
	Placebo (N=580) n (%)	Serelaxin (N=581) n (%)	Placebo (N = 62) n (%)	Serelaxin 30 µg/kg/day (N = 43) n (%)
Completed Day 180				
Yes	505 (87.1)	530 (91.2)	52 (83.9)	37 (86.0)
No	75 (12.9)	51 (8.8)	10 (16.1)	6 (14.0)
Primary reason for not completing study				
Death	65 (11.2)	41 (7.1)[3]	8 (12.9)	3 (7.0)
Withdrew Consent from Follow-up	9 (1.6)[1,2]	9 (1.5)[1,2]	2 (3.2)	2 (4.7)
Lost to Follow-up	1 (0.2)	1 (0.2)	0	1 (2.3)

[1] Patients who withdrew consent from follow-up are patients who both withdrew consent from contact and withdrew consent for access to hospital records.

[2] Vital status was determined for 6 of these 18 patients through public records or regular office visits as permitted by local regulations.

[3] One patient, who withdrew consent, died on Day 104 is therefore not included as withdrawn due to death in the disposition table

Source: [SCE-Table 3-7, Table 3-3]

Recruitment

The study was conducted at 96 centres in 11 countries: 10 centres in Argentina, 4 centres in France, 7 centres in Germany, 7 centres in Hungary, 9 centres in Israel, 6 centres in Italy, 5 centres in Netherlands, 9 centres in Poland, 8 centres in Romania, 4 centres in Spain, 27 centres in United States of America. The first patient was enrolled on 11-Oct-2009 (first patient first visit) and the last patient completed the trial on 14-Aug-2012 (last patient last visit). Although AHF is a common disorder, 96 centres recruited and treated 1161 patients in a period of 28 months, averaging 12 patients per centre and in each centre 1 patient every 71 days.

Conduct of the study

The protocol was amended 3 times after study initiation. The assessment of the trial is based on the final amended version. The amendments (including the addition of exclusion criterion #20 on hypersensitivity) are not believed to have influenced the validity of the trial.

The CSR of RELAX-AHF lists 1064 significant protocol violations (Listing 16.2.2-1) in 215/580 (37.1%) placebo and 233/581 (40.1%) serelaxin patients. The Applicant has given reassurance that very general terms like 'Any serious breach of the conditions and principles of Good Clinical

Practice', refer to administrative deficiencies only. It is not necessary to exclude the data of these patients from the final analysis.

Baseline data

The population in the trial is well-representative of the target population for the drug as defined in the proposed SmPC section 4.1

The majority of participants were elderly, and subjects up to 97 years of age were included. Participation of non-Caucasians was minimal; this point is addressed in the RMP. As subjects were sought with normal or elevated BP, a history of hypertension was present in 87% of subjects. Atrial fibrillation, ischaemic cardiac diseases, and heart failure were also frequently reported. Baseline medications seem in line with current recommendations for these patients (Table **3**).

Table 3 Demographic and baseline disease characteristic summary by treatment group – Study Pre-RELAX-AHF and RELAX-AHF (ITT analysis set)

		RELAX-AHF		Pre-RELAX-AHF	
Parameter	**Statistic**	**Placebo N=580**	**Serelaxin N=581**	**Placebo N=61**	**Serelaxin 30 µg/kg/day N=42**
Age (years)	Mean (SD)	72.5 (10.8)	71.6 (11.7)	68.4 (9.9)	71.6 (9.2)
Gender – n (%)	Male	357 (61.6)	368 (63.3)	40 (65.6)	18 (42.9)
	Female	223 (38.4)	213 (36.7)	21 (34.4)	24 (57.1)
Race – n (%)					
American Indian or Alaska Native		0	1 (0.2)		
Asian		2 (0.3)	2 (0.3)		
Black or African American		23 (4.0)	29 (5.0)	3 (4.9)	0 (0.0)
Native Hawaiian or Pacific Islander		0	1 (0.2)		
White		552 (95.2)	544 (93.6)	58 (95.1)	42 (100)
Multi-Racial		1 (0.2)	1 (0.2)		
Other		2 (0.3)	3 (0.5)		
Systolic BP at baseline (mmHg)	n'	578	577		
	Mean (SD)	142.1 (17.0)	142.2 (16.2)	147.5 (20.3)	150.3 (19.5)
HF hospitalisation (in the past year)	n (%)	181 (31.2)	216 (37.2)	18 (29.5)	16 (38.1)

		RELAX-AHF		Pre-RELAX-AHF	
Parameter	**Statistic**	**Placebo N=580**	**Serelaxin N=581**	**Placebo N=61**	**Serelaxin 30 µg/kg/day N=42**
Number of hospitalisations in past year	n'	180	214	n/a	n/a
	Mean (SD)	1.5 (1.13)	1.7 (1.48)		
Days since discharge from last hospitalisation	n'	156	196		
	Mean (SD)	125.2 (123.6)	118.1 (112.8)	149.7 (114.2)	109.4 (103.9)
Most recent ejection fraction < 40%	n (%)	295 (54.7)	303 (54.9)	19 (44.2)	15 (53.6)
NYHA* (most recent prior to admission)					
I	n (%)	11 (2.6)	12 (2.7)	2 (3.3)	0
II	n (%)	140 (33.0)	164 (37.5)	16 (26.2)	6 (14.3)
III	n (%)	198 (46.7)	191 (43.7)	23 (37.7)	17 (40.5)
IV	n (%)	72 (17.0)	63 (14.4)	12 (19.7)	14 (33.3)
hsTroponin T levels (µg/L)	n'	541	533	**	**
Geometric mean		0.0361	0.0341		
NT-pro-BNP (pg/L)	n'	551	550		
Geometric mean		5003.5	5125.5		
Medical history		n (%)	n (%)		
Hypertension		510 (87.9)	496 (85.4)	50 (82.0)	38 (90.5)
Stroke or other cerebrovascular event		84 (14.5)	73 (12.6)	13 (21.3)	8 (19.0)
Peripheral vascular disease		82 (14.1)	73 (12.6)	6 (9.8)	8 (19.0)
Malignancy		38 (6.6)	41 (7.1)	2 (3.3)	2 (4.8)
Mitral stenosis		6 (1.0)	8 (1.4)	1 (1.6)	0
Mitral regurgitation		182 (31.4)	179 (30.8)	14 (23.0)	13 (31.0)
Ischaemic heart disease		307 (52.9)	296 (50.9)	41 (67.2)	33 (78.6)

		RELAX-AHF		Pre-RELAX-AHF	
Parameter	**Statistic**	**Placebo N=580**	**Serelaxin N=581**	**Placebo N=61**	**Serelaxin 30 µg/kg/day N=42**
Atrial fibrillation/flutter		305 (52.6)	297 (51.1)	26 (42.6)	18 (42.9)
Diabetes mellitus		272 (46.9)	279 (48.0)	30 (49.2)	22 (52.4)
Congestive Heart Failure (CHF) within the last 1-month prior to admission		424 (73.1)	437 (75.2)	53 (86.9)	38 (90.5)
Angina pectoris		66 (11.4)	72 (12.4)	20 (32.8)	11 (26.2)
Cigarette smoking		81 (14.0)	72 (12.4)	11 (18.0)	5 (11.9)
Hyperlipidaemia		313 (54.0)	304 (52.3)	33 (54.1)	21 (50.0)
Pacemaker		58 (10.0)	63 (10.8)	7 (11.5)	5 (11.9)
Biventricular pacing		52 (9.0)	61 (10.5)	5 (8.2)	2 (4.8)
Auto. internal cardiac defibrillator		75 (12.9)	79 (13.6)	7 (11.5)	5 (11.9)

* New York Heart Association Classification
n' – patients with measurements
*classification was determined 1 month prior to admission
** In Pre-RELAX-AHF no hs troponin assay was used but I/T troponin was measured.
Source: [SCE-Table 3-1, Table 3-2, Table 3-4 and Table 3-5]

Randomisation has worked well and no important differences between the treatment groups were found.

The ITT and safety sets were defined as usual. In this trial, they were largely similar. Two 'Per protocol' sets were defined to address protocol deviations. Analyses in these sets are presented in the CSR. As they are similar to the main analyses, the results are not further discussed in this overview AR.

Numbers analysed

Additional exploratory analyses were conducted to evaluate the robustness of the findings and to assess the role of compliance and dose adjustment with the treatment regimen in the results. These analyses excluded further from the FAS population patients who had any of the major protocol deviations from the lists below. Two per-protocol analysis sets (PPS) were defined:

(1) PPS1 excluding only patients with pre-randomisation protocol deviations identified in the SAP, and

(2) PPS2 excluding patients with both pre-randomisation and post-randomisation protocol deviations specified in the SAP.

The following major pre-randomisation deviations excluded patients from PPS1:

- Screening blood pressure measurement <125 mm Hg (deviation of Inclusion Criterion 3)
- BNP < 350 pg/mL or NT-pro-BNP <1400 pg/mL (deviation of Inclusion Criterion 4)
- Randomised more than 16 hours from presentation (deviation of Inclusion Criterion 5)
- Use of disqualifying IV vasodilators, positive inotropes, vasopressors or mechanical support during screening (deviation of Exclusion Criterion 4)
- Known significant pulmonary disease (deviation of Exclusion Criterion 6)
- AHF due to known significant valvular disease as defined in protocol (deviation of Exclusion Criterion 7)
- AHF due to current (at the time of screening) acute coronary syndrome (deviation of Exclusion Criteria 12, 13)
- AHF due to significant arrhythmia as defined in protocol (deviation of Exclusion Criteria 14)

Additionally, the following post-randomisation deviations excluded subjects from PPS2:

- Non-compliance with study drug administration, i.e., receipt of less than 75% of the intended amount of study drug. For the primary Likert dyspnoea efficacy endpoint during the first 24 hours, the minimum duration of study drug infusion required is 18 hours. For the 3 remaining efficacy endpoints, the minimum duration of study drug infusion required is 36 hours, i.e. 75% of the intended amount. Subjects whose dose of study drug was appropriately reduced or discontinued will not be excluded.
- Failure to reduce or discontinue study drug administration in the presence of a blood pressure decrease event.

Patients were analysed by the group to which they were randomised. Key primary and secondary efficacy endpoints, as well as Day 180 mortality were examined in both PPS1 and PPS2. Patients who were missing the baseline dyspnoea VAS score were excluded from the PP analyses of the VAS AUC to Day 5 endpoint.

As presented in Table 22, there were no major differences between the ITT set (serelaxin: N=581; placebo: N=580) and the Safety set (serelaxin: N=568; placebo: N=570). The Safety set consisted of all patients who received treatment and patients were summarized based on the actual treatment received. There were 14 and 9 patients in the serelaxin and placebo groups, respectively, who were included in the ITT set, but excluded from the Safety set because they did not receive any study medication (reasons included patient refusal, physician discretion, or SBP <100 mmHg). One patient randomised to placebo who received serelaxin, was summarised under serelaxin for safety evaluation.

Table 4 Analysis sets – n (%) of patients

	Placebo	Serelaxin	Total
Intent-to-Treat (ITT) Set [1]	580	581	1161
Actual Treatment Received [2]			

• Placebo	570 (98.3)	0 (0.0)	570 (49.1)
• Serelaxin	1 (0.2)	567 (97.6)	568 (48.9)
• Not treated	9 (1.6)	14 (2.4)	23 (2.0)
Full Analysis Set (FAS) [3]	562 (96.9)	560 (96.4)	1122 (96.6)
Per Protocol Set 1 (PPS1) [4]	532 (91.7)	538 (92.6)	1070 (92.2)
Per Protocol Set 2 (PPS2) [5]	513 (88.4)	509 (87.6)	1022 (88.0)

[1] ITT Set includes all randomised patients.
[2] Safety Set includes all randomised patients who received any amount of study drug. Patients will be analysed as treated.
[3] FAS Set includes all randomised patients who were treated with any amount of study drug, and did not have any of 5 pre-specified major pre-randomisation eligibility protocol deviations, as defined in Section 9.7.2. Patients will be analysed as randomised.
[4] PPS1 Set includes all randomised patients who were treated with any amount of study drug, and did not have any major pre-randomisation protocol deviations, as defined in Section 9.7.2. Patients will be analysed as randomised.
[5] PPS2 Set includes all randomised patients who were treated with any amount of study drug, and did not have any major pre- and post-randomisation protocol deviations, as defined in Section 9.7.2. Patients will be analysed as randomised.
Source: PT-Table 14.1-1

The CHMP concluded that in this study the ITT and safety sets were defined as usual. In this trial, they were largely similar. Two 'Per protocol' sets were defined to address protocol deviations. Analyses in these sets are presented in the CSR. As they are similar to the main analyses, the results are not further discussed in this AR.

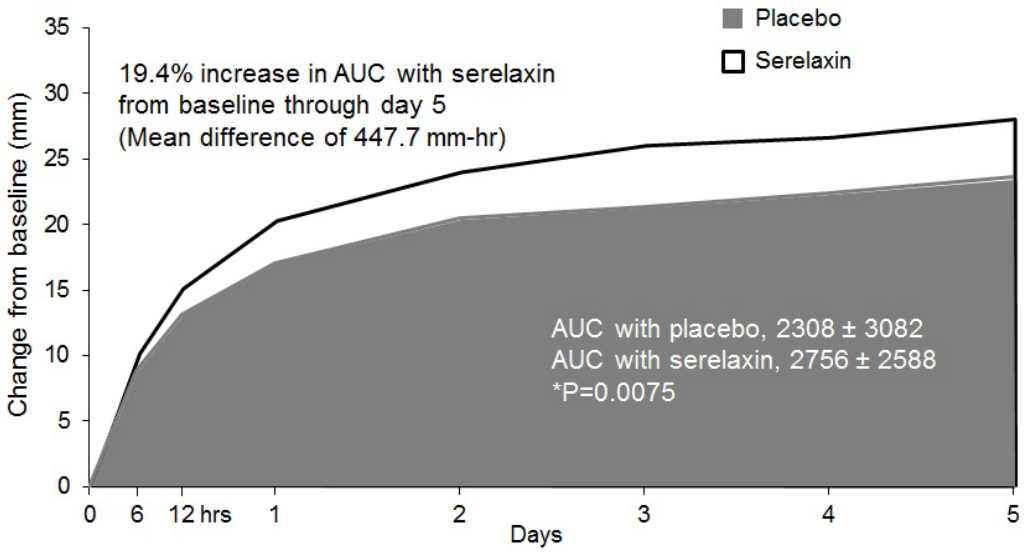
Outcomes and estimation

The first co-Primary Endpoint, the mean AUC of change from baseline in VAS through Day 5 was 2756 mm-hours and 2308 mm-hours in the serelaxin and placebo groups, respectively. The mean difference in VAS AUC between treatment groups was 447.7 mm-hours (95% CI 120.0, 775.4; t-test p=0.0075). Applying the Hochberg procedure as specified in the protocol, this allowed concluding superiority of serelaxin over placebo for dyspnoea relief. Several problems with the evaluation of this endpoint were evaluated:

Imputation

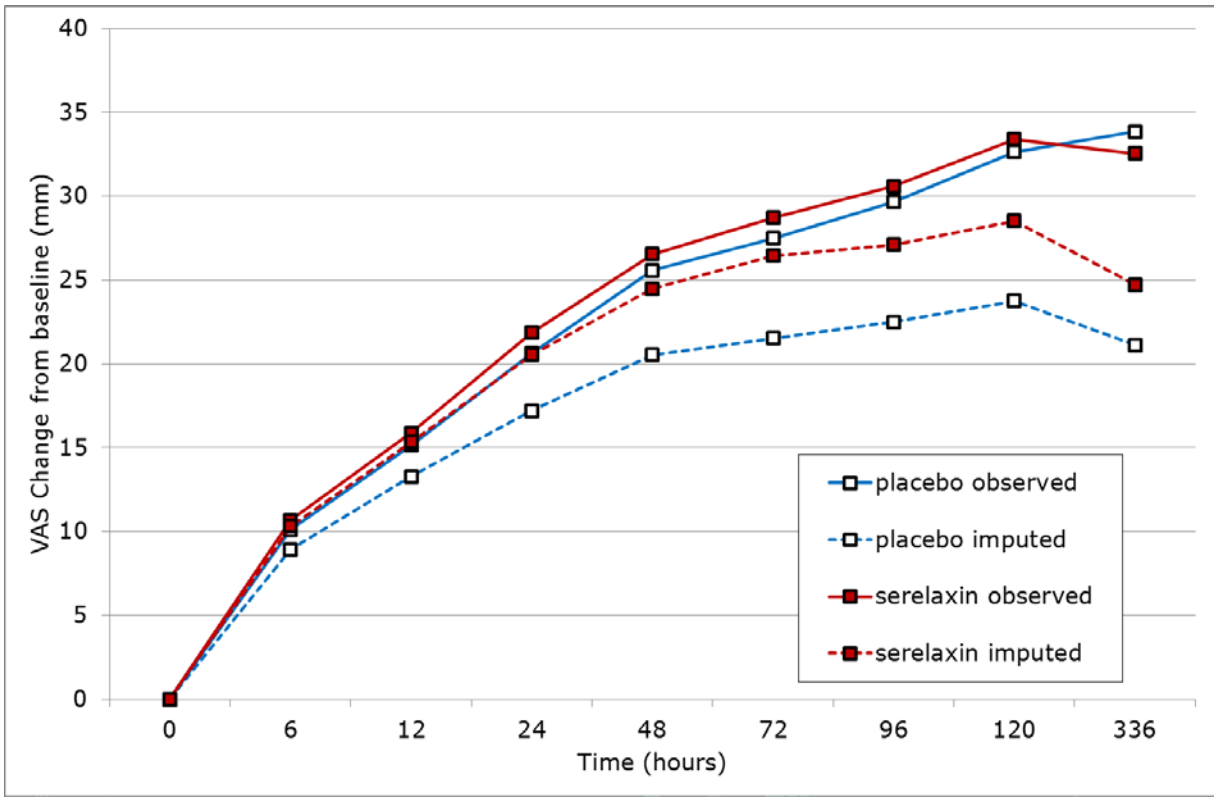
The results are driven by the values that were imputed after the subject was classified as 'Worsening Heart Failure' (WHF). Figure 3 shows the AUCs as they were used for the primary endpoint analysis. In Figure 4 (drafted by assessor), these same imputed VAS data are shown (dotted lines, non-linear X-axis extended to Day 14). In addition, the actually observed (non-imputed) data are shown (solid lines). The treatment effect in the observed data is much smaller than after imputation.

Figure 3 Mean change from baseline (mm) of dyspnoea Visual Analogue Scale (VAS) – Study RELAX-AHF (ITT analysis set)



*P-value is based on a two-sided two sample t-test for serelaxin vs. placebo comparing area under the mean curve (AUC, mm-hours) of change from baseline in dyspnea visual analog scale (VAS) through Day 5. Source: [SCE-Figure 3-1]

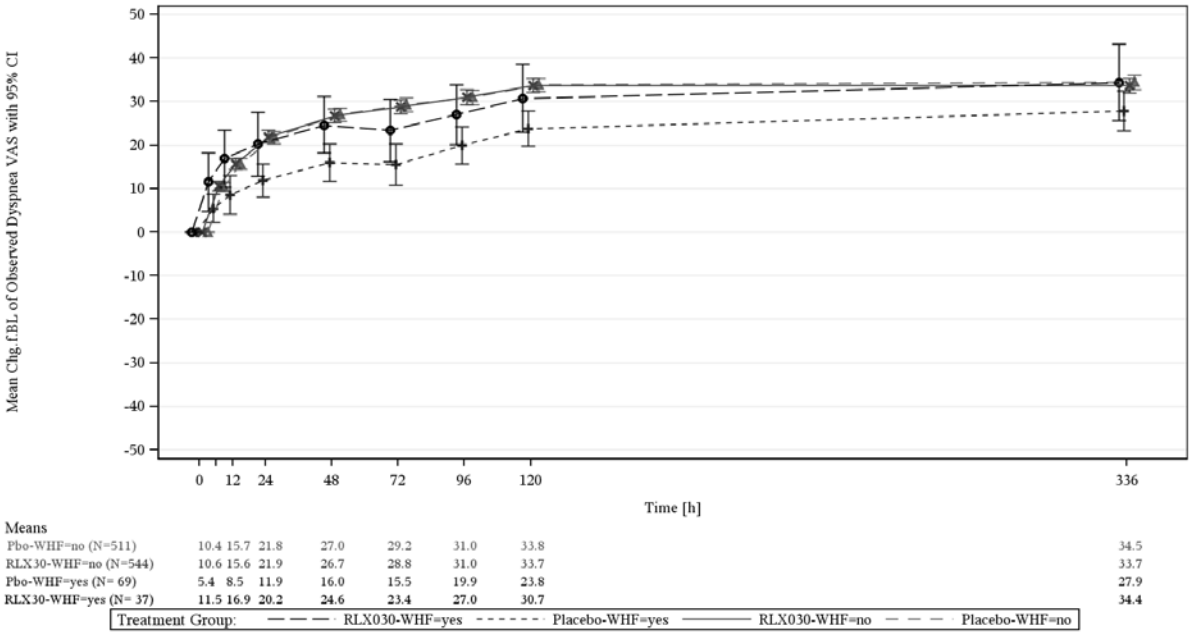
Figure 4 VAS in RELAX-AHF showing observed and imputed data



Notes: Non-linear X-Axis. Dotted lines correspond to **Figure** 3

Figure 5 and Figure 6 show the mean time course of dyspnea VAS stratified by experience of WHF through Day 5 and by treatment group using observed data and imputed data respectively.

Figure 5 Change from Baseline of Dyspnea VAS by WHF through Day 5 and treatment group: Observed data - Population: Intent-to-Treat Set

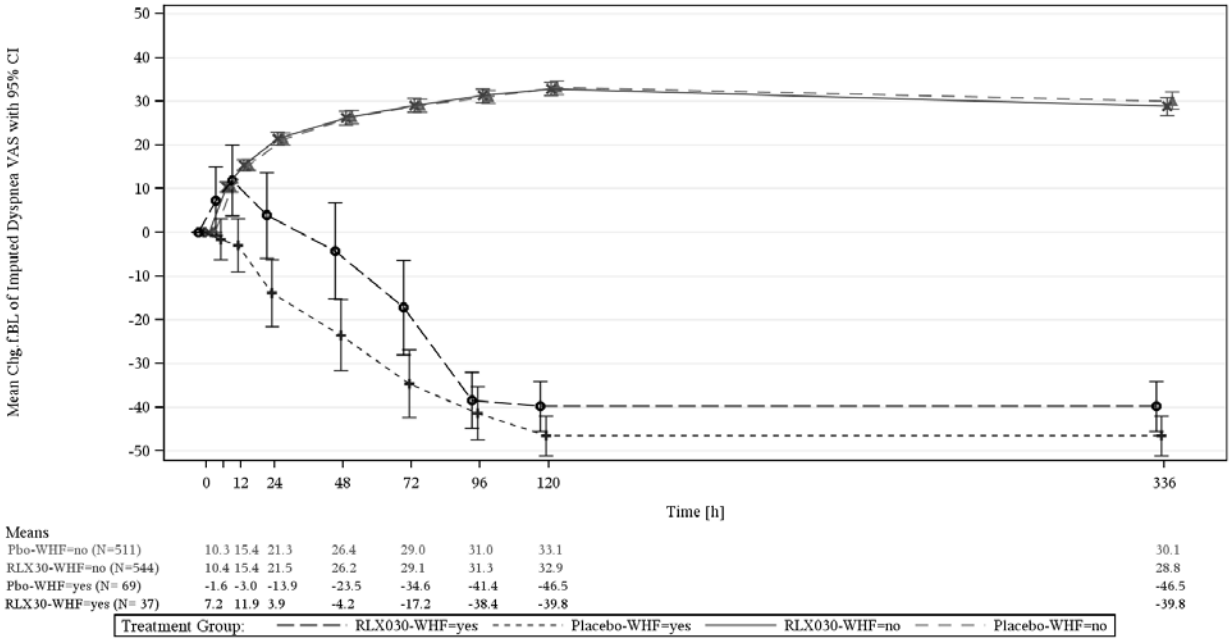


Note: Observed VAS data is presented, without any imputations, LOCF, linear interpolation, or baseline imputation

Note: WHF is defined as having an event through Day 5.

Source: [SCS-Appendix 1 Figure 132-1]

Figure 6 Change from Baseline of Dyspnea VAS by WHF through Day 5 and treatment group: Imputed data - Population: Intent-to-Treat Set



Note: Imputed VAS data (as in the primary analysis) is presented; this includes LOCF, linear interpolation, baseline imputation, and worst post-baseline imputation for patients from WHF or

death onwards
Note: WHF is defined as having an event through Day 5.
Source: [SCS-Appendix 1 Figure 132-2]

Both figures indicate that there is virtually no difference in mean VAS scores between treatment groups in the group of patients who did not experience WHF through Day 5.

The Applicant has justified the imputations, explaining that a WHF event and associated rescue therapy, would make a 'fair' evaluation of the treatment effect of relaxin impossible. Therefore, after such an event, the worst VAS value that was observed in the trial was imputed at all time-points after WHF. This imputed value was zero. However, in reality, the patients did not feel so dyspnoeic and the dyspnoea levels in the serelaxin and placebo groups were quite comparable. It is clear that the VAS endpoint actually measured WHF, not dyspnoea.

The Applicant has failed to show that the clinical state (symptomatic burden) of the patient at time of WHF and the impact of administered rescue therapy justify ignoring the subsequent VAS values that were observed. Although the diagnosis of WHF may have prognostic significance, this does not indicate symptomatic improvement or worsening. Bearing all these factors in mind, a reasonable ITT approach after WHF would be to impute missing values within the stratum of WHF patients (but not discard any values that were actually observed). The results of such an analysis would be very similar to Figure 5

Statistical analysis

Figure 7 shows a histogram of all observed VAS scores during the trial. It is clear that multiples of 5 and especially multiples of 10 occur more frequently than expected. The VAS worksheet, as reproduced in the CSR and below (Figure 8), shows that the VAS instrument had tick marks at 10, 20 etc. millimetres, which could explain this. This observation suggests that the VAS results in this trial were not a continuous, approximately normally distributed variable, but rather an ordinal scale. With the Day 121 responses, the Applicant did not document validation of the instrument before the trial. Still, the Applicant has provided an extensive post-hoc analysis of the performance of the VAS instrument which provides reassurance as to its usability for this MAA.

Figure 7 Histogram of all VAS dyspnoea values RELAX-AHF

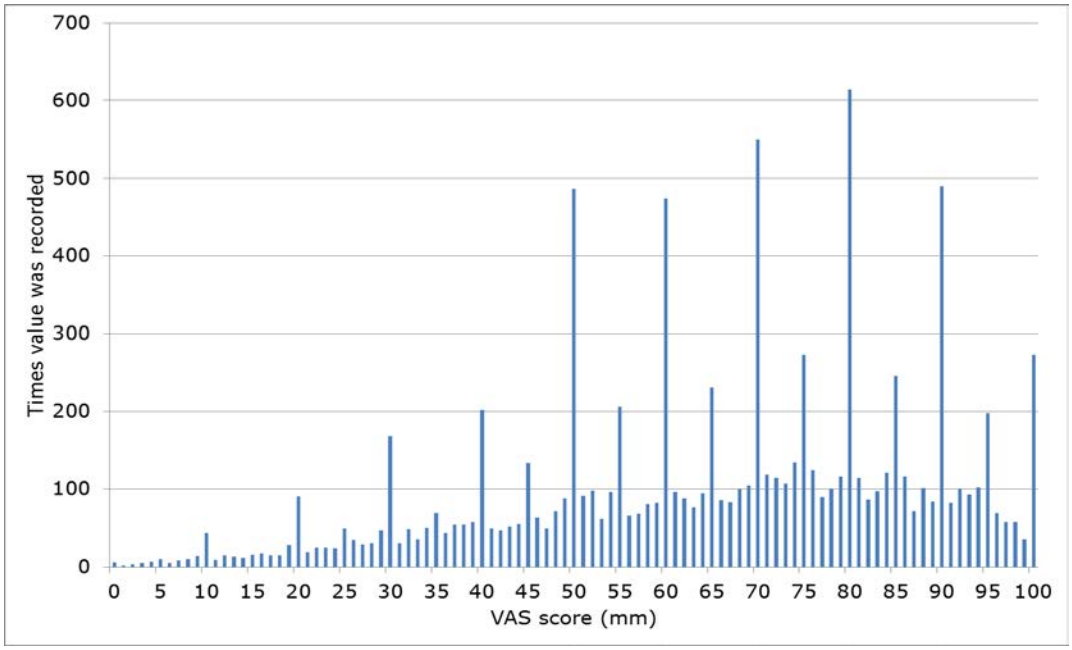


Figure 8 VAS tool used in RELAX-AHF

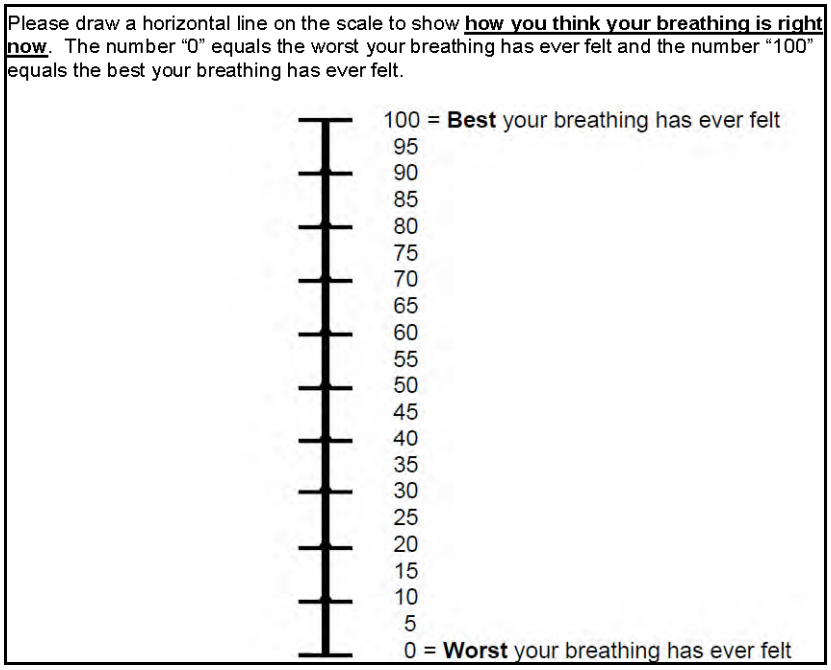
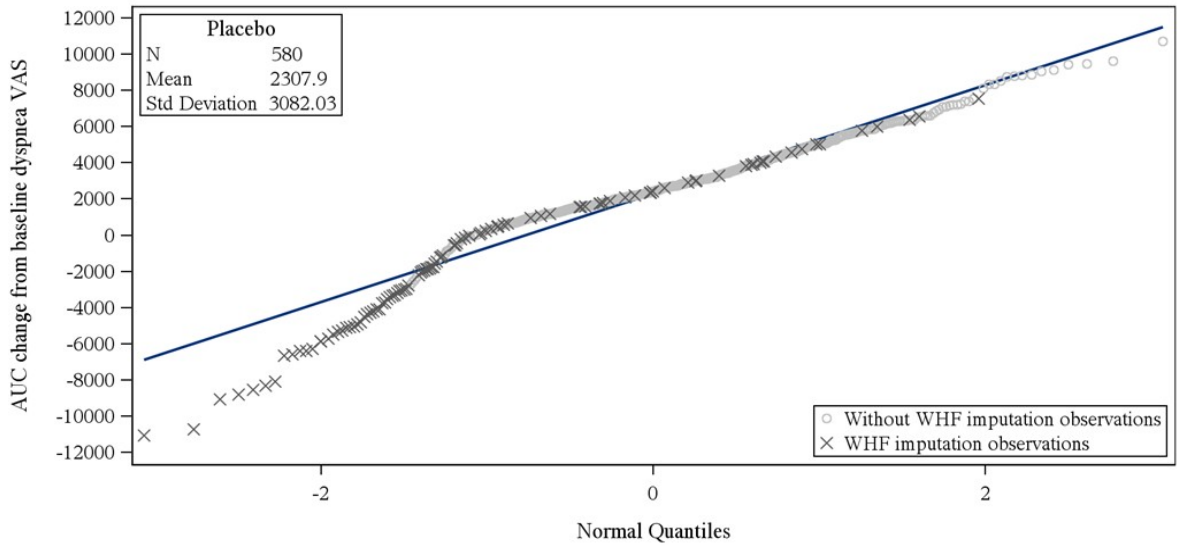
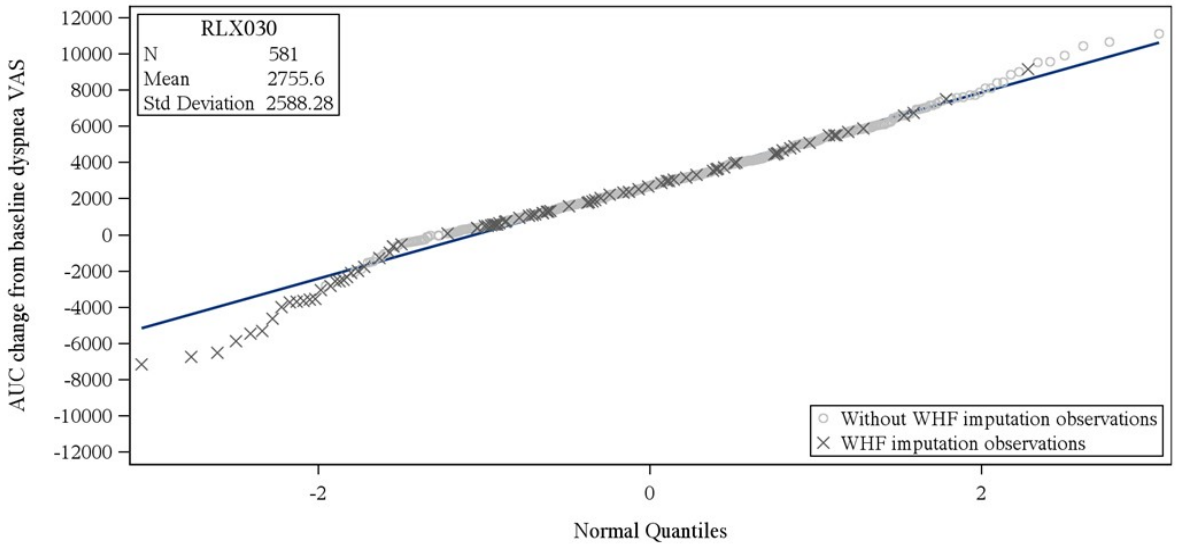


Figure 9 plot of area under the curve (AUC, mm-hr) of change from baseline of dyspnea visual analog scale (VAS) from baseline to Day 5 (population: Intent-to-Treat Set)

Placebo treatment group



Serelaxin 30 µg/kg/day treatment group



Source: [SCS-Appendix 1 Figure 100c-2]

Because of the large number of imputed zero values, the assumption of normality for the resulting VAS data, and possibly also for the corresponding AUC VAS data, was further investigated. A Q-Q plot of area under the curve (AUC, mm-hr) of change from baseline of dyspnoea VAS is shown in Figure 9.

The p-value associated with the Shapiro-Wilk test was below the predefined alpha-level of 0.005, suggesting a departure from normality. This departure is also visible in the above Q-Q plots, clearly showing a deviation from normality on the negative side, which is most likely due to imputation with the worst observed score after death or WHF. As defined in the protocol, the applicant provided a Wilcoxon test “to be reported as well” which failed to show a significant treatment difference.

However the Applicant argued that the t-test can still be considered as the primary test for drawing conclusions from the study. Indeed, with randomisation and with larger sample sizes, through the central limit theorem, t-tests are relatively robust to deviations from normality of individual subjects' data. This is supported by the randomisation-based t-test, which produced a p-value close to that of the primary analysis. Furthermore, the Shapiro-Wilk statistics in are close to 1. This indicates that the data distribution is close to normal even though the p-values are below 0.0001. With larger sample sizes, it is not uncommon that Shapiro-Wilk detects a small deviation from normality and produces a high Shapiro-Wilk statistic coupled with a low p-value. In conclusion, it is agreed with the Applicant that the t-test is relatively robust to deviations from the normal distribution and that the t-test can be accepted for the primary analysis.

Clinical relevance

The clinical relevance of the AUC of VAS change of baseline as reported is not clear. The AUC-difference that was termed clinically relevant in the sample size calculation was not reached. The sample size was adequate to detect a minimum clinically meaningful treatment difference of 468 mm-hour (4 mm difference across time points on average, by trapezoidal rule, assuming no difference at baseline and 4 mm from 6 hours to Day 5). Compared to a mean improvement in VAS of 30 or more (Figure 4) this difference seems rather limited.

The second co-Primary Endpoint, dyspnoea by Likert scale, did not reach statistical significance. The requirement of moderate or marked improvement of dyspnoea at each of the three time points of 6, 12, and 24 hours was reached similarly in both trial groups. (placebo:150/580 (25.9%), serelaxin: 156/581 (26.9%), p=0.702, Chi-square test). The applicant has stressed that the Likert scale and the VAS score are distinct entities. In this trial, the main difference is the timeframe for the observation (VAS: 0-5 days, Likert: 6-24 hours). The Likert scale endpoint worked as a responder analysis and required moderate or marked improvement at all the measured endpoints.

The Likert endpoint as used in the trial was not so sensitive to the WHF imputation, because WHF affected only 4% of subjects at the 24 hour time point. For the Likert endpoint, the impact of imputation was also less than for the VAS, because WHF-subjects were counted as 'did not reach moderate or marked improvement' (or 'non-responder').

In additional documentation (Patient Reported Outcomes report) supplied with the responses to the CHMP D 120 List of Questions, the Applicant has shown that the VAS and the Likert results show an acceptable level of correlation, meaning that the patients have understood the questions and usually responded in the same direction. The fact that in the primary analysis the VAS endpoint was positive and the Likert endpoint was not positive confirms that the VAS endpoint was driven primarily by the WHF imputations and that the clinical relevance (e.g. in terms of responders) was rather limited.

The secondary endpoint Days Alive and Out of Hospital did not reach statistical significance (p=0.3682). The numerical outcome was slightly in favour of serelaxin (48.3 vs. 47.7 days). Although the components 'duration of index hospitalisation' (8.9 vs. 9.5 days) and 'average time dead' (1.2 vs. 1.8 days) worked in favour of serelaxin, re-hospitalisations counted in favour of placebo (2.6 vs. 1.9 days).

The other secondary endpoint CV Mortality or HF/RF Rehospitalisation showed a similar outcome, because most death and re-hospitalisations were for CV or renal reasons. The HR for serelaxin vs. Placebo was 1.02 (95% CI: 0.74, 1.41; p=0.89). CV deaths were 27 (placebo) vs. 19 (serelaxin) and HF/RF re-hospitalisations were 50 (placebo) vs. 60 (serelaxin) yielding HRs of 0.70 (95% CI: 0.39, 1.26; p=0.23) and 1.21 (95% CI: 0.83, 1.76; p=0.32) respectively.

The Applicant correctly mentions that subjects who have died cannot experience re-hospitalisation, and thus these risks are competing. The finding could imply that although both serelaxin and placebo patients were frail, some of those treated with serelaxin survived to hospitalisation while their placebo-treated counterparts died. However, it could be expected that a genuine improvement in physical condition should improve both mortality and re-hospitalisations. Because death is a competing event for hospitalisation, the applicant provided analyses using the cumulative incidence function. The results were close to the original analyses using Kaplan-Meier estimates and lead to the same conclusions.

Data on re-hospitalisations between Day 60 and 180 were not collected.

Exploratory endpoints

A very large number of exploratory efficacy endpoints were investigated, sometimes at multiple time points or with multiple approaches (e.g. percentage responders and time-to-event). Some endpoints have been combined in various ways. Although hypothesis generation is the only valid justification for these endpoints, the hypotheses that could have been generated are sometimes difficult to imagine.

CV death through Day 180 was one of these exploratory endpoints and was reduced in serelaxin patients compared to placebo. Mortality is discussed under safety.

The biomarkers that were studied, hs-cTnT, Cystatin C and NT-proBNP, all show favourable changes in serelaxin patients compared to placebo. In all cases, these favourable changes were related to a better outcome for mortality through Day 180. The Applicant claims that these biomarkers show (protection against) organ damage and thus explain the mortality findings. It is however not clear how this organ protection would be the result of vasodilatation as caused by serelaxin. As was shown in the PD trials, renal blood flow was increased by serelaxin, but not cardiac index.

Worsening heart failure (WHF) was assessed by the physicians and defined as worsening signs and/or symptoms of HF that required an intensification of IV therapy for HF or mechanical ventilatory or circulatory support. WHF through Day 5 occurred in 106/1143 patients (9.3 %), more frequently in placebo patients (69/573, 12.0%) than in serelaxin patients (37/570, 6.5%; p<0.001). As discussed above, through the imputation rules, this was the parameter that actually made the difference. In an additional analysis, based on this trial, the applicant has shown that WHF increases the risk of a worse outcome by Day 180 in this trial.

Serelaxin patients were prescribed less furosemide than placebo patients (161 mg vs. 213 mg). Nevertheless, weight loss through Day 3 (both groups 2.0 kg) was similar and slightly more (placebo v. serelaxin) at Day 5 (3.0 vs 2.7 kg) and Day 14 (3.6 vs 3.0 kg). This suggests that serelaxin may have had diuretic effects in these patients. However, in the PD study RLX030A2202, no effect on diuresis or natriuresis could be concluded.

While the applicant has treated diuretic dose primarily as an outcome measure, the Applicant investigated also if higher-dose diuretic usage affected the outcomes of the trial. In an analysis of outcomes (VAS dyspnoea, weight change, renal function, potassium) stratified by cumulative dose of furosemide through Day 5, it was shown that the results were not driven by furosemide dose.

Summary of main efficacy results

The following Table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table Summary of efficacy for trial RELAX-AHF

Title: A phase II/III, multicentre, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of Relaxin in subjects with AHF		
Study identifier	RLX.CHF.003 (RELAX-AHF)	
Design	Randomisation within 16 hours after hospitalisation for AHF. Eligible patients were randomized in a 1:1 ratio to receive either IV placebo or serelaxin in a double-blind manner for 48 hours	
	Duration of main phase:	48 hours treatment. Observations for primary endpoint through Day 5, for secondary endpoint through Day 60 for exploratory and safety endpoint through Day 180.
	Duration of Run-in phase:	N/A
	Duration of Extension phase:	N/A
Hypothesis	Superiority Primary endpoints were combined using Hochberg approach Secondary endpoints were only tested if primary endpoint was achieved and combined using Hochberg approach Exploratory endpoints (18): No adjustment for multiplicity	
Treatments groups	Placebo	Placebo, N = 580
	Serelaxin	Serelaxin 30 µg/kg/day, N = 581

Endpoints and definitions	Co-Primary endpoint	VAS AUC	Area Under the Curve (AUC) representing the change in patient-reported dyspnoea from baseline measured by a 100-mm Visual Analogue Scale (VAS) through Day 5
	Co-Primary endpoint	Likert	Moderately or markedly better patient-reported dyspnoea relative to the start of study drug on the 7-point Likert scale at 6, 12 and 24 hours (at all 3 time-points).
	Secondary endpoint	DAOOH	Days alive and out of hospital through Day 60
	Secondary endpoint	CV death or rehosp	Cardiovascular death or rehospitalisation due to HF or RF through Day 60.
Study period	First patient enrolled: 11-Oct-2009 (first patient first visit) Last patient completed: 14-Aug-2012 (last patient last visit)		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Placebo	Serelaxin
	Number of subjects	580	581
Primary endpoints	VAS AUC (mean) mm h	2308	2756
	95% CI	2057, 2559	2545, 2966
	Likert scale (n (%)) Moderately or markedly improved at 6, 12, and 24 h timepoints	150 (25.9%)	156 (26.9%)

Secondary endpoints	DAOOH	47.7	48.3
	95% CI	46.7, 48.7	47.3, 49.2
	CV death or rehosp (Kaplan-Meier estimate %)	13.0	13.2
	95% CI	10.5, 16.1	10.7, 16.3
Effect estimate per comparison		Comparison groups	Serelaxin v Placebo
primary endpoints	VAS AUC	Mean difference	447.7
		95% CI	120.0, 775.4
		P-value (t-test)	0.0075
		P-value (Wilcoxon rank sum test)	0.082
	Likert scale (n (%))	P-value (Chi-Square test)	0.70
secondary endpoints	DAOOH	P-value (Wilcoxon rank sum test)	0.37
	CV death or rehosp	Hazard Ratio	1.02
		95% CI	0.74, 1.41
		P-value (log rank test)	0.89
Analysis description	**Exploratory analysis**		
Analysis population and time point description	Pooled Safety Set (Pre-Relax AHF and RELAX-AHF)		
Descriptive statistics	Treatment group	Placebo	Serelaxin

and estimate variability	Number of subject	631	610
Exploratory endpoint	Mortality Day 180 N, Kaplan-Meier estimate %	72 11.7%	44 7.4%
Effect estimate per comparison		Comparison groups	Serelaxin v Placebo
Exploratory endpoint	Mortality Day 180	Hazard Ratio	0.61
		95% CI	0.42, 0.89
		P-value	0.0110

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

Efficacy trials in the special populations of severe renal impairment and hepatic impairment were not performed. A paediatric investigation plan is agreed, but no results are available.

In the RELAX-AHF trial, most participants were elderly subjects. The CSR provides data for the following age groups: <65, ≥ 65, <75 and ≥ 75 years. The results in the elderly populations are similar to the younger populations.

As the number of non-white participants was very low, the subgroup analysis by race was non-informative.

Supportive study(ies)

N/A

2.5.3. Discussion on clinical efficacy

Study RELAX-AHF was the single pivotal trial submitted in this dossier. This was a randomised controlled trial, in which the patients with AHF were treated with placebo or serelaxin (nominally 30 µg/kg/day intravenously) for up to 48 hours, on top of standard of care. The inclusion criteria were not strict about 'acuteness' of the heart failure episode. It is not clear how early the treatment should be initiated to provide benefit optimally. Randomisation was allowed until 16 hours after presentation, but as most symptomatic improvement is made during the first hours of hospitalisation (e.g. Figure 3), the moment of initiation of a symptomatic therapy (like serelaxin) will affect the maximum benefit that can be achieved.

The guideline-preferred endpoint (*EMA Guidance on clinical investigations of medicinal products for the treatment of cardiac failure/Addendum on acute heart failure [CPMP/EWP/2986/03]*) for trials in AHF is 30-Day all-cause mortality, but symptomatic relief (dyspnoea relief), which was chosen in RELAX-AHF, can be an acceptable endpoint too. The EMA scientific advice (2010) stressed the importance of fast relief of dyspnoea, as measured in this trial by the Likert scale endpoint at 6, 12 and 24 hours. Contrary to the advice, the Applicant chose a parallel assessment of persistent dyspnoea relief (0-5 Days) in a co-primary endpoint. These endpoints were combined using the Hochberg procedure, which implied that the trial could be declared positive on persistent dyspnoea relief alone, as in fact happened. The predefined level of statistical significance, which was agreed in the scientific advice, for an application based on a single pivotal trial, was not met. The Applicant believes that the beneficial effects on mortality by Day 180 could compensate for this lack of statistical persuasive power, but this is not agreed. Also other conditions for an application based on a single clinical trial are not fulfilled, e.g. internal validity (VAS v. Likert) and clinical relevance of the primary effect size.

The included patients are representative of non-hypotensive AHF patients that are hospitalised. However, consistent with clinical practice, most subjects had acute decompensated chronic heart failure, with limited data on other HF classes. The majority of participants were elderly persons, and subjects up to 97 years of age were included. A history of hypertension was present in 87% of subjects. Randomisation has worked well and no important differences between the treatment groups were found. Serelaxin showed greater efficacy in patients with HF-pEF as shown by the concurrent significant improvement of Likert and VAS scales compared to patients with HF-rEF where a marginal, questionable clinical effect, was noted only on the VAS scale.

In RELAX-AHF the comparator was inactive placebo and it is a matter of fact that the protocol produced post randomization heterogeneities between the study arms, the most important of these being a major difference in arterial pressure throughout the infusion period of Serelaxin {difference of systolic pressure >5 mmHg at 9 hours [serelaxin 15.9 (95%CI: 14.5-17.3) and placebo 10.1 (95%CI: 8.6-11.6]}. Arterial pressure is a main component of cardiac afterload, a determinant of heart work and a key target for therapy. Actually some of the outcomes observed during the hospital phase can be influenced by the differences in afterload generated by the study protocol and deserve careful evaluation and discussion. Although the scientific advice EMA/CHMP/SAWP/784780/2010 accepted placebo as a comparator for this trial, the advice required that the protocol would define use of vasodilatators such as nitrates, thus preventing treatment imbalances between arms. However, the study protocol did not lead to a reasonable use of i.v. nitroglycerine (no difference compared to serelaxin group) while the vasolilator effect of Serelaxin resulted in the above mentioned difference in arterial pressure and heart workload. The placebo arm was therefore, during the infusion phase of the protocol, undertreated compared to the active arm.

The first co-Primary Endpoint, the mean AUC of change from baseline in VAS through Day 5 was 2756 mm-hours and 2308 mm-hours in the serelaxin and placebo groups, respectively. The mean difference in VAS AUC between treatment groups was 447.7 mm-hours (95% CI 120.0, 775.4; t-test p=0.0075). Applying the Hochberg procedure as specified in the protocol, superiority of serelaxin over placebo for dyspnoea relief was concluded.

The trial was powered to detect a mean difference of 4 mm in the VAS endpoint as measured at different time points for dyspnoea relief (captured as AUC); an effect size of 15 to 20% was

considered clinically relevant by the trial Executive Committee but the clinical relevance of this choice is not further justified. As can be learnt from Figure 4, most subjects improve about 30 mm in 5 days as effect of the current standard of care. According to SCE Table 3-8, the mean improvement in the placebo group in RELAX-AHF (with all imputations) was 2308 mm hr, corresponding to an average of 19,7 mm. The treatment effect corresponds to a mean improvement of 3.83 mm, 19.4% of the placebo response.

Even in the main analysis on the intention-to-treat population, zero values were imputed for VAS (and 'markedly worse' for Likert) after WHF, although these data were not truly missing as they were collected anyhow. The Applicant has justified this, stating that the assessments were not really representative of the investigative drug's treatment effect. However, it seems to contradict the principles of an intention-to-treat analysis.

The Applicant states that imputation with the worst observed VAS score is justified, because imputing with missing values is too optimistic, dyspnoea is not measured at the moment WHF occurs, and because the clinical course after WHF is fundamentally different. Although based on these arguments it is reasonable to conclude that treating the VAS scores after WHF as missing may be appropriate, it does not justify imputation with the worst observed value. The same argumentation could be used to justify imputation using baseline values, but this model was not chosen by the applicant.

The Applicant has discussed extensively the prognosis of subjects experiencing WHF but has failed to show that the clinical state (symptomatic burden) of the patient at time of WHF and the impact of administered rescue therapy justify ignoring the subsequent VAS values that were observed. Although the diagnosis of WHF may have prognostic significance, this does not indicate symptomatic improvement or worsening. Bearing all these factors in mind, a reasonable ITT approach after WHF would be to impute missing values within the stratum of WHF patients (but not discard any values that were actually observed). The results of such an analysis would be very similar to Figure 5.

In the sensitivity analysis on the VAS AUC data, imputing values after WHF as the patient's baseline value, the mean AUC was 2748 mm-hr for the placebo group and 2922 mm-hr for the serelaxin group, resulting in a difference of 174 mm-hr (95% CI: -85, 434; p = 0.19 by t-test), corresponding to a mean difference in VAS of 1,5 mm at all time points. Other sensitivity analyses provided similar results, which were all not statistically significant.

The second co-Primary Endpoint, dyspnoea by Likert scale, did not reach statistical significance. The requirement of moderate or marked improvement of dyspnoea at each of the three time points of 6, 12, and 24 hours was reached similarly in both trial groups (placebo:150/580 (25.9%), serelaxin: 156/581 (26.9%), p=0.702, Chi-square test). The applicant has stressed that the Likert scale and the VAS score are distinct entities. In this trial, the main difference is the timeframe for the observation (VAS: 0-5 days, Likert: 6-24 hours). In the scientific advice, the early timeframe was considered most important and in the Pre-RELAX trial, only the early timeframe showed a statistically significant result (Table 2). The Likert scale endpoint worked as a responder analysis and required moderate or marked improvement at the chosen endpoints. Contributing factors to the apparent difference between VAS and Likert outcomes include the early (6-hour) Likert assessment that was required to become a 'responder', the non-parametric approach to evaluation of the Likert-scale endpoint (not as powerful as the parametric test for

VAS) and the cumulative effect of WHF which biased the VAS endpoint but much less the Likert-scale endpoint, because WHF affected only 4% of subjects at the 24 hour time point and also because WHF-subjects were counted as 'did not reach moderate or marked improvement' (or 'non-responder') for the Likert endpoint.

No clear benefits were shown in the secondary endpoints, where length of the index hospitalisation and CV mortality favoured serelaxin, but re-hospitalisations favoured placebo. Because death is a competing event for hospitalisation, the applicant provided analyses using the cumulative incidence function. The results were close to the original analyses using Kaplan-Meier estimates and lead to the same conclusions.

The biomarkers that were studied, hs-cTnT, Cystatin C and NT-proBNP, show favourable changes in serelaxin patients compared to placebo. The Applicant claims that these biomarkers show (protection against) organ damage and thus explain the mortality findings. It is however not clear how this organ protection would be the result of vasodilatation as caused by serelaxin. A clear result on cardiac output or renal blood flow, as may be provided by the on-going PD trials, would help in understanding these interesting findings.

Worsening heart failure (WHF) was assessed by the physicians and defined as worsening signs and/or symptoms of HF that required an intensification of IV therapy for HF or mechanical ventilatory or circulatory support. WHF through Day 5 occurred more frequently in placebo patients (69/573, 12.0%) than in serelaxin patients (37/570, 6.5%; $p<0.001$). As discussed above, through the imputation rules, this was the parameter that actually made the difference. In an additional analysis, based on this trial, the applicant has shown that WHF increases the risk of a worse outcome by Day 180 in this trial.

Serelaxin patients were prescribed less furosemide than placebo patients (161 mg vs. 213 mg). Nevertheless, weight loss through Day 3 (both groups 2.0 kg) was similar and slightly more (placebo v. serelaxin) at Day 5 (3.0 vs 2.7 kg) and Day 14 (3.6 vs 3.0 kg). Also in the PD studies, no clear diuretic or natriuretic effect of serelaxin could be concluded.

More generally, the treating physicians' opinion of the serelaxin patients' condition seems to have been more positive than of the placebo-treated patients. This is evident in the findings on physical examination (of these, "dyspnoea on exertion", "oedema" and "rales" showed improvement, "orthopnoea" and "jugular venous pulse" did not), the (less) prescribing of diuretics, more frequently starting of ACE inhibitors (placebo: 4.1%, serelaxin 7.7%), less use of IV inotropic medications, shorter hospital stay and less WHF. It may be difficult to capture this 'opinion' numerically. Moreover, the clear BP effects of serelaxin may have hampered the blindness of the study, especially in the patients where the BP effect was most pronounced.

Additional expert consultation

At Day 180 List of Outstanding Issues (LoOIs) the CHMP decided to consult the Cardiovascular Scientific Advisory Group (SAG CVS) and adopted the List of Questions to the SAG CVS at this point of time. A SAG CVS was convened on 9 December 2013. The CHMP questions to SAG and SAG experts' answers are presented below:

Question 1

The SAG is asked to comment on the clinical relevance of the findings in RELAX-AHF as well as phase II studies with respect to

a) relief of dyspnoea, taking into account the

- **clinical relevance of the improvement on the dyspnoea VAS scale taking into account the estimate of the effect size in relation to the predefined level of clinical significance,**
- **impact of imputations that were applied when rescue therapy was given (WHF),**
- **lack of significant effect using the Likert-scale in RELAX-HF,**

b) reduction of WHF taking into account its definition and characteristics in RELAX,

c) numerical difference in mortality at 6 months, taking into account the

- **strength of statistical evidence,**
- **lack of an effect at 60 days,**
- **discrepancy between the outcomes of hospitalisation for heart failure and mortality,**

d) changes in haemodynamics,

e) relevance of the background therapy in the (PRE) RELAX-AHF trial in particular concerning the use of nitrates.

Answer to question 1:

a) The Visual Analogue Scale (VAS) is a tool not used in every day clinical care. Thus it is difficult to translate a small reduction into clinical benefit.

A 4 mm reduction in VAS, as proposed in the study protocol, seems to be a very small improvement and unlikely to be clinically relevant, especially since most patients used 5 or 10 mm increments in the VAS to mark their dyspnoea status as it has been applied in scaled design. Moreover, the predefined level of 4 mm has not been reached (3.84 mm have been reached). 1 mm improvement on dyspnoea VAS, representing the non-imputed VAS results, is certainly not clinically relevant.

The imputation approach chosen by the applicant of zeroing the VAS scores at the time of WHF occurrence (which was based on physician judgment) and on further time points up to five days does not render the VAS results as a measurement of dyspnoea alone. It combines a patient derived symptomatic score with a physician derived signs and symptom measurement and does not seem to measure exactly the primary endpoint variable. To impute the value of zero seems to be a too extreme approach and carrying it beyond the time of WHF for the rest of the measurement points seems too strict. The imputed VAS looses statistical significance if a more meaningful value would be used for imputation instead of zero.

The Likert scale provided the assessment of the shorter observation period (24 hours) as compared to VAS scale. Furthermore, the interpretation was done on the basis of responder status analysis rather than as a numerical evaluation. The Likert scale results are in line with the VAS results when the VAS values are not imputed.

b) It was noted that WHF was not among the primary or secondary endpoints in the protocol, as it was an exploratory endpoint only. Though the occurrence of WHF in the RELAX trial could be seen as a marker of prognosis, its impact on the course of heart failure is not completely understood based on the per protocol definition of WHF.

The reduction in WHF with serelaxin is difficult to interpret, since the definition criteria used in the study do not account for the underlying reason, i.e. do not take into account heart rate, occurrence of atrial fibrillation, peripheral oedema or infections like the occurrence of pneumonia.

The SAG members felt, that, although the increase in diuretics alone did not trigger the event, the definition of WHF was not detailed enough in the protocol to draw firm conclusions. Nevertheless, WHF, properly defined with strict adjudication criteria measured at the time of deterioration, is seen as a valuable clinical variable for future studies.

c) The observed difference in mortality endpoint at 6 months lacks a pathophysiological explanation given only a short term administration of the drug (48 hours). It was an exploratory parameter and the study was not powered for measuring mortality as an efficacy endpoint. It was rather used as a safety parameter. The result was largely driven by CV mortality; however it has not been shown that a difference in the pump failure related events contributed to a relevant extent. Stroke contributed significantly to the overall difference and death attributed to heartfailure was even higher in patients receiving Serelaxin. The SAG acknowledged however that the mortality difference was observed in both the PreRELAX and Relax trials.

The increase in the mortality difference over time cannot be explained on the basis of the so far known biological activity of the compound and the short duration of infusion. Thus it would be warranted to study this parameter in a properly designed prospective trial.

d) A clear doses response is being questioned, at least in relation to symptoms and blood pressure (BP).

The overall hemodynamic findings including lowering of filling pressures are in line with decongestion. The lack of cardiac output increase (CI) was discussed and not felt to be a matter of major clinical concern, however it was not clearly understood given the reduction in systemic vascular resistance.

e) Only a small cohort of the study population was given nitrates as part of the background therapy, which was lower than expected based on the available usage data (e.g. Euro Heart Survey) and common practice. The reason is probably partly investigators- and partly protocol–driven (iv. nitrates in patients with SBP below 150 mm Hg were not allowed). It is not clear to which extent and in which direction the low use of nitrates might have affected the results.

Question 2

Based on the responses to question 1, do the SAG members regard the efficacy of serelaxin as clinically meaningful in the targeted population, taking into account that

the studied population may not be representative for the total population, or are further confirmatory data needed?

Answer to question 2:

The population investigated is representative for a sizeable subset of patients with AHF with preserved or elevated systolic blood pressure. The early inclusion up to 16 hrs after admission is found appropriate. No data are available for patients with entry SBP under 125. This should be reflected in the indication.

The claim of symptomatic improvement has been questioned and is not sufficiently supported by the results (see answer to Q1).

Question 3

Do the members regard the safety characteristic of serelaxin as manageable in clinical routine including patients with normal-low blood pressure and those at risks for coronary steal syndromes?

Answer to question 3:

The effect of serelaxin on haemoglobin is not well understood. The observed hemodynamic response lacks a clear dose response relationship and thus dose adjustment would be difficult /impossible in clinical practice.

No data are available in patients with SBP below 125 mm Hg. A meaningful subset of patients with ischemic heart disease have been entered in RELAX without angina or myocardial infarction / ischemia being reported in a larger number of pts. Thus coronary steal seems not to be a major concern. However, data on the occurrence of myocardial infarction have not been collected beyond day 14.

2.5.4. Conclusions on the clinical efficacy

Although the Applicant has declared the trial to be positive, only the first co-primary endpoint (VAS AUC for dyspnoea relief) met the predefined significance criteria. The responder analysis (Likert scale), most sensitivity analyses and the secondary endpoints measuring mortality and hospitalisation did not demonstrate benefits. The methodology used to assess the VAS endpoint has measured WHF instead of direct dyspnoea relief and the reported results are considered inconclusive in terms of clinical benefit.

2.6. Clinical safety

Patient exposure

The primary dataset used for the evaluation of safety is the pooled safety population of Pre-RELAX-AHF and RELAX-AHF, consisting of all patients who received at least one dose of trial medication. This population consists of 737 AHF patients who received serelaxin and 631 patients who received placebo. It is agreed to use this pooled dataset, excluding the Phase 2 and PD trials. These latter trials recruited a somewhat different population that was small and

RLX.CHF.001 included no placebo group (Table 5). The recently concluded Phase 2 trials (A2201, A2202), which were reported at Day 121, are not included in the integrated safety analysis.

Table 5 Summary of patients in serelaxin development program

	Relaxin	Placebo	Total
HF pooled	737	631	1368
HF, not pooled	23	4	27
All HF	760	635	1395
Non HF	590	287	877
PK (A2101 & A2103)	81	8	89
Non-HF & PK	671	295	966
HF and non-HF	1431	930	2361

The total number of patients exposed to serelaxin and analysed is 1431. The information retrieved from the 'legacy' and healthy volunteer trials is supplementary only.

The RELAX program yields a database of 737 exposed patients in the proposed population and dose. The EMA scientific advice (EMA/CHMP/SAWP/784780/2010) considered that the size of the database might be sufficient. It was difficult to set safety requirements or evaluate the adequacy of the data set to exclude all important, but rare, safety elements without knowing the magnitude of benefit. Marginal benefit might require additional safety data compared to evidence for marked clinical improvement. Absence of a detrimental effect on mortality was important and the Company was advised to seek follow-up advice once the Phase 3 trials results would be available.

In the pooled RELAX dataset, 610 patients were treated with serelaxin according to the proposed dosing schedule. In RELAX AHF, dose reductions for low blood pressure occurred in 103/570 (18.1%) placebo patients and 167/568 (29.4%) patients in the serelaxin group. Other patients have received less study drug than prescribed due to AEs, consent withdrawal or medication errors. In the end, 376 of 578 (66.2%) patients received at least 98% of the 'calculated dose' in RELAX-AHF.

Adverse events

As per protocol, in the Pre-RELAX-AHF trial, AEs and SAEs were assessed up to Day 30. The RELAX-AHF study protocol required the collection of all AEs through Day 5 after initiating treatment and all SAEs through Day 14. These choices were based on the short-term IV exposure of serelaxin. In the Pre-RELAX-AHF trial, 38% of the AEs were reported after 5 days (assessor's count); similarly, 34% of the SAEs were reported after Day 15. Thus, the collection period for both SAEs and AEs was rather short, especially where the Applicant claims a beneficial effect after 180 days.

Disease-related events

In both Pre-RELAX-AHF and RELAX-AHF, a list of AEs was pre-specified as 'disease-related events' or DREs (indicated with an asterisk), which were considered as part of the natural history of the underlying disease and therefore were to be anticipated for the condition. For 'expected' DREs the usual 24-hour sponsor notification did not apply (but SUSARs were still reported expeditely). DREs appear together with (S)AEs in the listings that are provided. It is confusing that some terms appear both as an (S)AE and DRE (e.g. hypotension). However, this 'DRE' concept does not further impact the safety analysis and is acceptable.

AEs by SOC

Approximately 50% of the patients in the serelaxin groups experienced at least one AE from study drug initiation to Day 5 with a slightly lower percentage compared to the placebo group. The most commonly reported primary SOCs were cardiac disorders (201 patients, 14.7%), metabolism and nutrition disorders (158 patients, 11.5%), gastrointestinal disorders (119 patients, 8.7%) and vascular disorders (118 patients, 8.6%). The incidence of cardiac disorders was lower in the serelaxin groups compared to the placebo group (table 6).

Table 6 Incidence of adverse events by system organ class from Study Drug Initiation to Day 5 (Population: Safety Set - Pooled RELAX-AHF and Pre-RELAX-AHF)

System Organ Class	Placebo (N=631) n(%)	RLX030 30 µg/kg/day (N=610) n(%)	RLX030 <=30 µg/kg/day (N=650) n(%)	All Serelaxin (N=737) n(%)	Total (N=1368) n(%)
Patients With at Least One AE	**344 (54.5)**	**302 (49.5)**	**331 (50.9)**	**377 (51.2)**	**721 (52.7)**
Blood And Lymphatic System Disorders	7 (1.1)	11 (1.8)	11 (1.7)	12 (1.6)	19 (1.4)
Cardiac Disorders	105 (16.6)	77 (12.6)	87 (13.4)	96 (13.0)	201 (14.7)
Congenital, Familial And Genetic Disorders	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.1)
Ear And Labyrinth Disorders	4 (0.6)	2 (0.3)	2 (0.3)	2 (0.3)	6 (0.4)
Endocrine Disorders	3 (0.5)	1 (0.2)	1 (0.2)	1 (0.1)	4 (0.3)
Eye Disorders	1 (0.2)	3 (0.5)	3 (0.5)	3 (0.4)	4 (0.3)
Gastrointestinal Disorders	61 (9.7)	48 (7.9)	54 (8.3)	58 (7.9)	119 (8.7)
General Disorders And Administration Site Conditions	42 (6.7)	34 (5.6)	37 (5.7)	42 (5.7)	84 (6.1)
Hepatobiliary Disorders	10 (1.6)	1 (0.2)	1 (0.2)	1 (0.1)	11 (0.8)
Immune System Disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Infections And Infestations	30 (4.8)	27 (4.4)	29 (4.5)	34 (4.6)	64 (4.7)
Injury, Poisoning And Procedural Complications	1 (0.2)	4 (0.7)	4 (0.6)	4 (0.5)	5 (0.4)
Investigations	45 (7.1)	34 (5.6)	35 (5.4)	41 (5.6)	86 (6.3)
Metabolism And Nutrition Disorders	74 (11.7)	72 (11.8)	77 (11.8)	84 (11.4)	158 (11.5)
Musculoskeletal And Connective Tissue Disorders	22 (3.5)	28 (4.6)	33 (5.1)	39 (5.3)	61 (4.5)

Neoplasms Benign, Malignant And Unspecified (Inc. Cysts And Polyps)	2 (0.3)	4 (0.7)	4 (0.6)	4 (0.5)	6 (0.4)
Nervous System Disorders	51 (8.1)	32 (5.2)	34 (5.2)	37 (5.0)	88 (6.4)
Psychiatric Disorders	34 (5.4)	23 (3.8)	23 (3.5)	27 (3.7)	61 (4.5)
Renal And Urinary Disorders	35 (5.5)	27 (4.4)	28 (4.3)	33 (4.5)	68 (5.0)
Reproductive System And Breast Disorders	0 (0.0)	2 (0.3)	3 (0.5)	4 (0.5)	4 (0.3)
Respiratory, Thoracic And Mediastinal Disorders	63 (10.0)	32 (5.2)	34 (5.2)	38 (5.2)	101 (7.4)
Skin And Subcutaneous Tissue Disorders	3 (0.5)	7 (1.1)	7 (1.1)	7 (0.9)	10 (0.7)
Vascular Disorders	52 (8.2)	36 (5.9)	49 (7.5)	66 (9.0)	118 (8.6)

Note: Patients are counted once per SOC
Note: Incident AEs are considered those AEs with an onset date and time after the initiation of study drug.
Note: 'Patients With at Least One AE' counts every patient, who experienced an AE episode in this interval
Source: [SCS-Appendix 1-Table 14.3.1-5]

AEs by PT and Causality

Hypokalaemia* (7.1% in serelaxin 30 µg/kg/day, 7.2% in serelaxin ≤30 µg/kg/day and 6.0% in placebo) and hypotension (1.6% in serelaxin 30 µg/kg/day, 1.5% in serelaxin ≤30 µg/kg/day and 0.2% in placebo) were the most common AEs reported by higher percentages of patients in the serelaxin dose groups compared to the placebo group, and with a difference of ≥1.0% between serelaxin 30 µg/kg/day group and the placebo group. No other AEs were reported with a difference in incidence ≥1% in any of the serelaxin dose groups above placebo (**Table 7**).

Table 7 Incidence of Adverse Events from study drug initiation to Day 5 (at least 1.0% in any group) (Population: Safety Set - Pooled RELAX-AHF and Pre-RELAX-AHF)

Preferred Term	Placebo (N=631) n(%)	Serelaxin 30µg/kg/d (N=610) n(%)	Serelaxin ≤30µg/kg/d (N=650) n(%)	All Serelaxin (N=737) n(%)
Subjects With at Least One AE	**344 (54.5)**	**302 (49.5)**	**331 (50.9)**	**377 (51.2)**
Hypokalaemia*	38 (6.0)	43 (7.1)	47 (7.2)	50 (6.8)
Cardiac Failure Congestive*	39 (6.2)	23 (3.8)	27 (4.2)	31 (4.2)
Blood Creatinine Increased*	26 (4.1)	17 (2.8)	18 (2.8)	23 (3.1)
Headache	33 (5.2)	16 (2.6)	17 (2.6)	19 (2.6)
Constipation	16 (2.5)	15 (2.5)	15 (2.3)	15 (2.0)
Chest Pain*	8 (1.3)	11 (1.8)	12 (1.8)	14 (1.9)
Diarrhoea	20 (3.2)	11 (1.8)	13 (2.0)	14 (1.9)
Dyspnoea*	25 (4.0)	11 (1.8)	12 (1.8)	14 (1.9)
Urinary Tract Infection	6 (1.0)	11 (1.8)	11 (1.7)	13 (1.8)
Hypoglycaemia	17 (2.7)	10 (1.6)	10 (1.5)	11 (1.5)

Hypotension	1 (0.2)	10 (1.6)	10 (1.5)	10 (1.4)
Hypotension*	13 (2.1)	10 (1.6)	18 (2.8)	31 (4.2)
Renal Failure*	25 (4.0)	10 (1.6)	11 (1.7)	14 (1.9)
Hyperuricaemia	10 (1.6)	8 (1.3)	8 (1.2)	8 (1.1)
Insomnia	10 (1.6)	8 (1.3)	8 (1.2)	9 (1.2)
Vomiting	7 (1.1)	8 (1.3)	9 (1.4)	10 (1.4)
Back Pain	3 (0.5)	7 (1.2)	9 (1.4)	9 (1.2)
Dizziness	12 (1.9)	7 (1.2)	8 (1.2)	8 (1.1)
Hypertension*	23 (3.6)	7 (1.2)	11 (1.7)	14 (1.9)
Anaemia	2 (0.3)	6 (1.0)	6 (0.9)	7 (0.9)
Asthenia	10 (1.6)	6 (1.0)	6 (0.9)	8 (1.1)
Hyperglycaemia	5 (0.8)	6 (1.0)	6 (0.9)	6 (0.8)
Non-Cardiac Chest Pain*	6 (1.0)	6 (1.0)	7 (1.1)	7 (0.9)
Pain In Extremity	6 (1.0)	6 (1.0)	8 (1.2)	9 (1.2)
Cardiac Failure*	9 (1.4)	5 (0.8)	6 (0.9)	9 (1.2)
Nausea	13 (2.1)	5 (0.8)	5 (0.8)	7 (0.9)
Phlebitis	7 (1.1)	5 (0.8)	7 (1.1)	7 (0.9)
Pneumonia	7 (1.1)	5 (0.8)	5 (0.8)	5 (0.7)
Confusional State	8 (1.3)	4 (0.7)	4 (0.6)	4 (0.5)
Ventricular Tachycardia*	12 (1.9)	4 (0.7)	6 (0.9)	7 (0.9)
Anxiety	6 (1.0)	3 (0.5)	3 (0.5)	4 (0.5)
Atrial Flutter*	6 (1.0)	3 (0.5)	6 (0.9)	6 (0.8)
Cough	10 (1.6)	2 (0.3)	2 (0.3)	3 (0.4)

* Disease-related event (DRE). The incidence across the two hypotension terms cannot be summed since a patient may have experienced an event in either category at different times during the study.

Note: Incident AEs are considered those AEs with an onset date and time after the initiation of study drug.

Source: [SCS-Table 2-2]

Potential ADRs were defined as those all-treatment emergent AEs through Day 5 that occurred with a 1% higher frequency in the serelaxin 30 µg/kg/day group compared to the placebo group in the pooled RELAX-AHF and Pre-RELAX-AHF population. Applying the 1% higher frequency vs.

placebo, the AEs of 'hypokalaemia' and 'hypotension' (reported as symptomatic and asymptomatic hypotension) were also identified as potential ADRs for serelaxin.

The vast majority of the AEs of Hypokalaemia were observed in the two AHF studies RELAX-AHF and CRLX030A2201. In contrast, events were only sporadically reported in other HF and non-HF trials, in which patients were exposed in part to even higher doses and for longer duration compared to serelaxin 30 µg/kg/day IV administered for up to 48 hours. In study RELAX-AHF, no baseline risk factors for developing hypokalaemia were identified except a slightly lower mean serum potassium level, which was well within the normal range. Kaplan-Meier estimates of the 'Time to first onset of the AE Hypokalaemia (days)' through Day 5 did not indicate that serelaxin poses an increased risk of Hypokalaemia compared to placebo. No clinically relevant changes in serum potassium through all HF and non-HF studies were identified.

The fact that these events mainly occurred in 2 AHF studies and the absence of a plausible mechanistic explanation make it likely that confounding factors in AHF patients, such as underlying disease and background therapy (e.g. diuretics) known to interfere with the physiological potassium balance, have contributed to these events.

It is agreed that no definite conclusions can be made with regard to hypokalaemia, based on currently available data. This issue will be explored further in an upcoming outcome study, CRLX030A2301, is mentioned in SmPC section 4.8 and in the RMP as an identified risk. Furthermore it is considered that patients with AHF will be treated with diuretics, thus prompting monitoring of electrolytes. Based on current data, this approach is sufficient.

Severity

The distribution of AEs by maximum severity was similar across the serelaxin treatment groups and placebo treatment group, and graded as mild (26.2 to 27.1% of patients), moderate (18.2 to 21.2% of patients) or severe (4.9% to 7.0% of patients). There were specifically fewer severe cardiac failure congestive events in the serelaxin dose groups (0.2 to 0.3%) compared with placebo (1.4%). Similarly, there were fewer events of moderate or severe grade renal failure AEs in the serelaxin dose groups compared with placebo.

Reversibility

There are no clinical data suggesting that serelaxin causes irreversible AEs.

Events of special interest

Non-clinical findings and findings from the 'legacy' trials are captured as 'events of special interest'.

AEs indicative of renal impairment were reported by a lower percentage of patients in the serelaxin 30 µg/kg/day dose group (5.9%) compared to the placebo group (9.2%) to Day 14.

The clinical presentation of the typical AHF patient often includes signs and symptoms of congestion of the liver, with periods of hypotension, which may lead to abnormalities in LFTs. **Hepatic events** were reported by a lower percentage of patients in the serelaxin 30 µg/kg/day dose group (0.8%) compared to the placebo group (2.5%).

Potential promotion of cancers is an AE of special interest based on theoretical grounds. There are no clinical data supporting this, but the SAE capturing period of 14 days is too short to

allow any conclusion. Based on the PRAC assessment, it was not necessary to include this as a potential risk in the RMP because it was considered too implausible.

There were four events of bone fracture in the serelaxin database. Two events occurred in the serelaxin arm in Pre-RELAX-AHF and occurred at Day 30 following serelaxin infusion of 10 µg/kg/day (finger fracture, 57 year old Male) and at Day 36 following infusion of 250 µg/kg/day (pelvic fracture, 82 year old male). Two events of bone fracture also occurred in the 30 µg/kg/day serelaxin arm in the RELAX-AHF study, both in the setting of falls (hip fracture in a 90 year old female on Day 4 and femoral neck fracture in an 85 year old male on Day 12); neither of these events was suspected to be drug-related. The event onset, location of fractures, and/or the circumstances of these cases (e.g., falls) make a causal relationship between serelaxin and these fractures unlikely. Based on the PRAC assessment, it was not necessary to include this as a potential risk in the RMP because it was not considered relevant to single dose administration in humans.

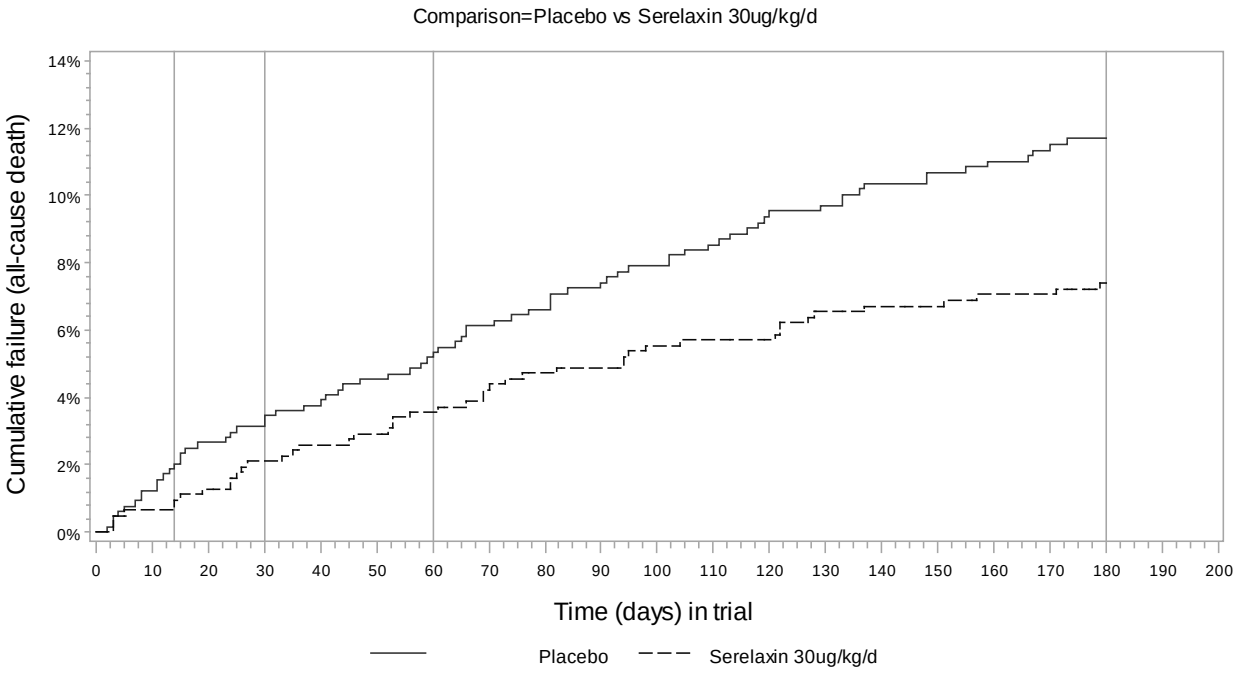
No adverse effects indicating arrhythmogenic or QT prolonging properties of serelaxin have been observed in clinical trials. In the pooled dataset of study Pre-RELAX-AHF and RELAX-AHF, no differences were observed in AEs related to cardiac arrhythmias.

Serious adverse event / deaths / other significant events

Deaths

A lower percentage of patients in the serelaxin dose group 30 µg/kg/day (44 patients, K-M estimate 7.4%) compared to the placebo group (72 patients, K-M estimate 11.7%) died due to all causes through Day 180 (hazard ratio (HR) = 0.61, 95% CI: 0.42, 0.89, p=0.0110) (**Figure 10**). K-M estimates of all-cause mortality were in favour of the serelaxin dose group 30 µg/kg/day (3.6%, 95% CI: 2.4, 5.5) compared to the placebo group 5.4%, 95% CI: 3.9, 7.5) at Day 60. This analysis is consistent in subgroups, with two notable exceptions: Baseline SBP < 130 mmHg (SBP > 125 mmHg was an inclusion criterion for the trials; placebo: 21/129 (17,0%); serelaxin 30 µg/kg/day: 19/108 (18,0%) HR 1.04, 95% CI 0.56-1.94) and Baseline eGFR ≥ 60 mL/min/m² (serelaxin 30 µg/kg/day: 11/171 (6,6%) placebo: 8/187 (4,4%); HR: 1.51, 95% CI: 0.61-3.74). The Applicant ascribes these findings to possible chance and this is accepted.

Figure 10 Kaplan-Meier plot of all-cause mortality through Day 180 (ITT set, pooled Pre-RELAX-AHF and RELAX-AHF)



Hazard ratio (hazard ratio<1.0 favours serelaxin) and 95% CI: 0.63 (0.43, 0.91), p-value=0.0134

Source: [SCE Figure 3-10]

Adjudicated causes of death are shown in Table 8.

A higher proportion of patients in the placebo group (53 patients, K-M estimate 9.4%) compared to the serelaxin group (34 patients, K-M estimate 6.0%) were reported as having deaths due to CV causes. The most commonly reported CV causes of death were heart failure/pump failure (37 patients, 3.3%), sudden death (24 patients, 2.2%). Heart failure/pump failure was reported by similar percentages of patients (3.6% in serelaxin and 3.1% in placebo), while sudden death was reported by a higher percentage of patients in the placebo group compared to the serelaxin group (3.0% in placebo vs. 1.5% in serelaxin.

CV Mortality was an exploratory efficacy endpoint in RELAX-AHF and all-cause mortality was a safety measure in the RELAX program. The potential benefit however, is important and the hypothesis is intriguing. It is not easy to link the primary pharmacology of serelaxin (as demonstrated in humans) to this potential mortality benefit. A similar benefit has not been shown for other vasodilatators like nitrates. Exploratory analyses presented in the dossier have linked the mortality finding to prevention of WHF, worsening renal failure and to biomarkers related to organ damage (Heart – troponin-T, Kidney – Cystatin-C) and congestion (NT-pro-BNP).

Table 8 Adjudicated causes of death in RELAX-AHF through Day 180.

		Placebo (N=570)	RLX030 (N=568)	Total (N=1138)
Best Available Classification of Cause of Death Through Day 180 [1]				
All causes	n (%)	64 (11.3)	41 (7.3)	105 (9.3)
Cardiovascular cause	n (%)	53 (9.4)	34 (6.0)	87 (7.7)
Heart Failure/Pump Failure	n (%)	17 (3.1)	20 (3.6)	37 (3.3)
Sudden Death	n (%)	16 (3.0)	8 (1.5)	24 (2.2)
Acute coronary syndrome	n (%)	1 (0.2)	1 (0.2)	2 (0.2)
Cardiac Procedure Complication	n (%)	1 (0.2)	0 (0.0)	1 (0.1)
Other Cardiac Death	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular Accident/Stroke	n (%)	8 (1.5)	1 (0.2)	9 (0.8)
Peripheral Vascular Disease	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Systemic Embolus	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary Embolus	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular Procedure Complication	n (%)	3 (0.6)	0 (0.0)	3 (0.3)
Other Vascular Death	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Renal Failure	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary	n (%)	2 (0.4)	0 (0.0)	2 (0.2)
Pneumonia	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Sepsis	n (%)	6 (1.2)	3 (0.6)	9 (0.9)
Other Infection	n (%)	0 (0.0)	2 (0.4)	2 (0.2)
Gastrointestinal	n (%)	0 (0.0)	1 (0.2)	1 (0.1)
Seizure	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Other Neurologic	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Hematologic	n (%)	1 (0.2)	0 (0.0)	1 (0.1)
Malignancy	n (%)	2 (0.4)	1 (0.2)	3 (0.3)
Other Non-cardiovascular	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Non-cardiovascular Procedure Complication	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Presumed Cardiovascular Death/Unknown	n (%)	7 (1.3)	4 (0.7)	11 (1.0)
Investigator Classification of Cause of Death Through Day 180				
All causes	n (%)	64 (11.3)	41 (7.3)	105 (9.3)
Cardiovascular cause	n (%)	50 (8.9)	34 (6.0)	84 (7.5)
Heart failure/pump failure	n (%)	18 (3.3)	18 (3.2)	36 (3.3)
Sudden death	n (%)	9 (1.7)	8 (1.5)	17 (1.6)
Acute coronary syndrome	n (%)	1 (0.2)	1 (0.2)	2 (0.2)
Cardiac procedure	n (%)	1 (0.2)	1 (0.2)	2 (0.2)
Other cardiac	n (%)	1 (0.2)	2 (0.4)	3 (0.3)
Cerebral vascular accident (CVA)/stroke	n (%)	6 (1.1)	2 (0.4)	8 (0.7)
Peripheral vascular disease	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Systemic embolus	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary embolus	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular procedural complication	n (%)	1 (0.2)	0 (0.0)	1 (0.1)
Other vascular death	n (%)	1 (0.2)	0 (0.0)	1 (0.1)
Renal	n (%)	1 (0.2)	1 (0.2)	2 (0.2)
Pulmonary	n (%)	3 (0.6)	0 (0.0)	3 (0.3)
Pneumonia	n (%)	2 (0.4)	0 (0.0)	2 (0.2)
Sepsis	n (%)	4 (0.8)	3 (0.6)	7 (0.7)
Other infection	n (%)	0 (0.0)	1 (0.2)	1 (0.1)
Gastrointestinal	n (%)	0 (0.0)	1 (0.2)	1 (0.1)
Seizure	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Other neurological	n (%)	3 (0.6)	0 (0.0)	3 (0.3)
Hematological	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Malignancy	n (%)	1 (0.2)	1 (0.2)	2 (0.2)
Other non-cardiovascular	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	n (%)	12 (2.3)	2 (0.4)	14 (1.3)

[1] Classification by CEC.
Note: Percentages represent Kaplan-Meier estimate of the Day 180 event rate.
Note: Table is based on data that include adjudicated CV deaths from Day 61 through Day 180.

The mortality findings are regarded as hypothesis-generating and the hypothesis that serelaxin improves the outcome for patients with AHF deserves further investigation

SAEs

A higher percentage of patients in the serelaxin 30 µg/kg/day dose group (92 patients, 15.1%) compared to the placebo group (82 patients, 13.0%) reported at least one SAE from study drug initiation to Day 14. Similar percentages of patients in each serelaxin dose group reported at least one SAE from study drug initiation to Day 14. The Applicant has not summarised the total number of SAEs. (**Table 9**).

Table 9 Incidence of Serious Adverse Events (SAEs) From Study Drug Initiation to Day 14 (Population: Safety Set - Pooled RELAX-AHF and Pre-RELAX-AHF)

System Organ Class	Placebo (N=631) n(%)	Serelaxin 30 µg/kg/d (N=610) n(%)	Serelaxin ≤30 µg/kg/d (N=650) n(%)	Serelaxin All (N=737) n(%)	Total (N=1368) n(%)
Patients with at least one SAE	**82 (13.0)**	**92 (15.1)**	**97 (14.9)**	**108 (14.7)**	**190 (13.9)**
Blood and Lymphatic System Disorders	3 (0.5)	1 (0.2)	1 (0.2)	1 (0.1)	4 (0.3)
Cardiac Disorders	45 (7.1)	39 (6.4)	42 (6.5)	44 (6.0)	89 (6.5)
Gastrointestinal Disorders	3 (0.5)	2 (0.3)	2 (0.3)	2 (0.3)	5 (0.4)
General Disorders and Administration Site Conditions	0 (0.0)	3 (0.5)	3 (0.5)	3 (0.4)	3 (0.2)
Hepatobiliary Disorders	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
Infections and Infestations	14 (2.2)	9 (1.5)	10 (1.5)	13 (1.8)	27 (2.0)
Injury, Poisoning and Procedural Complications	0 (0.0)	5 (0.8)	6 (0.9)	6 (0.8)	6 (0.4)
Investigations	1 (0.2)	2 (0.3)	2 (0.3)	2 (0.3)	3 (0.2)
Metabolism and Nutrition Disorders	1 (0.2)	6 (1.0)	7 (1.1)	8 (1.1)	9 (0.7)
Musculoskeletal and Connective Tissue Disorders	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	3 (0.5)	3 (0.5)	3 (0.5)	3 (0.4)	6 (0.4)
Nervous System Disorders	6 (1.0)	8 (1.3)	8 (1.2)	8 (1.1)	14 (1.0)
Psychiatric Disorders	0 (0.0)	3 (0.5)	3 (0.5)	3 (0.4)	3 (0.2)
Renal and Urinary Disorders	7 (1.1)	10 (1.6)	10 (1.5)	12 (1.6)	19 (1.4)

System Organ Class	Placebo (N=631) n(%)	Serelaxin 30 µg/kg/d (N=610) n(%)	Serelaxin ≤30 µg/kg/d (N=650) n(%)	Serelaxin All (N=737) n(%)	Total (N=1368) n(%)
Respiratory, Thoracic and Mediastinal Disorders	6 (1.0)	13 (2.1)	13 (2.0)	15 (2.0)	21 (1.5)
Skin and Subcutaneous Tissue Disorders	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Surgical and Medical Procedures	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Vascular Disorders	2 (0.3)	2 (0.3)	2 (0.3)	4 (0.5)	6 (0.4)

Note: Patients are counted once per SOC.

The most commonly reported primary SOCs were cardiac disorders (6.4% vs.7.1%), infections and infestations (1.5% vs. 2.2%), respiratory, thoracic and mediastinal disorders (2.1% vs. 1.0%) and renal and urinary disorders (1.6%vs. 1.1%) in the serelaxin 30 µg/kg/day dose group and placebo group, respectively. Cardiac failure* was reported by a higher percentage of patients in the serelaxin 30 µg/kg/day dose group (8 patients, 1.3%) compared to the placebo group (4 patients, 0.6%;) and the incidence of CHF through Day 14 when three related PTs of cardiac failure acute, cardiac failure congestive, and cardiac failure were combined were 22 patients (3.6%) vs. 19 patients (3.0%) in the serelaxin and placebo groups, respectively.

Respiratory, Thoracic and Mediastinal Disorders were the only SOC that occurred ≥1% more frequently in the serelaxin group (placebo 6/631 (1.0%) vs serelaxin 13/610 (2.1%)).

Laboratory findings

Haematology

In the pooled RELAX-AHF and Pre-RELAX-AHF studies, higher proportions of patients in the serelaxin group compared to the placebo group reported >20% decrease from baseline to Day 14 for haemoglobin (9 patients, 1.5% vs. 4 patients, 0.6%, respectively), haematocrit (10 patients, 1.6% vs. 4 patients, 0.6%, respectively) and red blood cells (RBC) (7 patients, 1.1% vs. 4 patients, 0.6%, respectively. It is not clear if these events occurred in the same patients.

On Day 2 in RELAX AHF, the median change from baseline for Haemoglobin was +0,1 g/dL in the placebo group vs -0,2 g/dL in the serelaxin group (RELAX AHF CSR, Table 14.3-6.1.1).

The applicant attributes these changes to haemodilution, which would be consistent with the vasodilation caused by serelaxin. However, the 25% increase in plasma volume after initiation of treatment for AHF required to explain a 20% drop haemoglobin seems not realistic. Moreover, median decreases in weight were similar in the placebo and serelaxin groups of RELAX AHF

Clinical Chemistry

In the RELAX-AHF study, in general, smaller percentages of patients had serum creatinine increases at any post-baseline visit in the serelaxin dose group 30 µg/kg/day compared to the

placebo group for increases ≥ 0.3 mg/dL (52.5% vs. 58.4%), ≥ 0.5 mg/dL (27.7% vs. 33.3%), ≥ 1.0 mg/dL (7.4% vs. 9.0%) and >50% increase from baseline (16.5% vs. 19.4%). This could be explained by a beneficial effect of serelaxin on the kidney or by differences in concomitant medication, e.g. diuretics.

In the Pre-RELAX AHF study, there was a trend towards more frequently increased creatinine levels in the group that received 250 µg/kg/day serelaxin (**Table 1**).

ECGs

ECGs were evaluated in a total of 4 studies at various time points during or after study drug administration: in study R9401 conducted in 30 patients with systemic sclerosis, in RLX.CHF.001 in 16 patients with CHF, study RLXN.C.002 in 12 patients with systemic sclerosis, and in a substudy in RELAX-AHF study conducted in 22 patients who met ECG analysis eligibility requirements. Across all of these studies, no significant or apparently drug related changes were noted in ECG results.

The RELAX-substudy did not meet is objective in terms of included patients. It can be assumed that most patients in the (Pre-)RELAX-AHF program, being on a cardiology ward, had frequent ECG examinations and important changes would have been captured as AEs. However, for a cardiology product, these data are very limited.

Pulse, respiratory rate, body temperature, weight

Vital signs data for RELAX-AHF and Pre-RELAX-AHF were not pooled. No significant differences were detected in pulse, respiratory rate, body temperature or weight.

In RELAX-AHF, median change from baseline in weight was similar in the serelaxin and placebo groups (Day 3: serelaxin = placebo = -2.0 kg).

Blood pressure

SBP > 125 mmHg at the time of screening was required for inclusion in the RELAX-AHF trial. Mean values for SBP were comparable between the 30 µg/kg/day serelaxin group (142.6 mmHg) and placebo group (142.4 mmHg) at baseline. As expected from the PD effect of serelaxin, SBP was significantly decreased in the serelaxin group compared to the placebo group within 30 min. from the start of the infusion, reached a maximum at 8 hours, and persisted during the rest of the infusion. At the end of the 48-hour infusion period, SBP values were 128.0 mmHg in the serelaxin group and 131.0 mmHg in the placebo group. SBP measurements were similar between the two groups by Day 4 (48 hours after cessation of infusion).

In both Pre-RELAX-AHF and RELAX-AHF, measures were proactively included in the protocol to manage confirmed blood pressure decrease events (**CBPDEs**). BP was to be monitored periodically during the 48-hour treatment with serelaxin, and the dose adjusted if the patient's BP dropped below defined levels, which was documented as a CBPDE. In the RELAX-AHF study protocol, dosing adjustment based on the severity of confirmed systolic BP decrease was mandated: If SBP >100 mmHg, but has decreased by >40 mmHg from pre-treatment value, adjust the serelaxin dose by reducing the infusion rate by 50% for the remainder of the 48-hour infusion time. If SBP <100 mmHg, permanently terminate serelaxin infusion. This algorithm is also recommended in the SmPC.

In the safety population of RELAX-AHF, a greater proportion of patients on serelaxin (167 patients, 29.4%) compared to placebo (103 patients, 18.1%) experienced CBPDE during the 48-hour infusion period. The proportion of placebo patients experiencing a CBPDE is surprisingly high; this may be related to (recovery from) the stress associated with AHF and hospitalisation.

SBP at baseline did not predict CBPDE. In the relaxin group, the mean SBP at baseline for patients with and without CBPDE were 144.1 and 142.0 mmHg respectively.

CBPDEs resulted in dose reduction (75 patients, 44.9% vs. 43 patients, 41.7%), discontinuation of study drug (107 patients, 64.1% vs. 71 patients, 68.9%) or a dose reduction followed by a discontinuation (16 patients, 9.6% vs. 12 patients, 11.7%) in the serelaxin group and placebo group, respectively. Following dosing adjustment, there was partial recovery of the SBP during the first 60 minutes by approximately 10 mmHg. The recovery in the placebo group was somewhat less. Five hours following event onset, the mean SBP reduction was 31.9 mmHg (from 47.8 mmHg at event onset) in the dose reduction group and 25.1 mmHg (from 41.7 mmHg at event onset) in the discontinuation of study drug subgroup. Most CBPDEs had no or few symptoms.

All-cause mortality (Day 180) and HF/RF rehospitalisation were higher in patients in the relaxin group of RELAX-AHF who experienced a CBPDE compared to those who did not (**Table 10**).The effect was more pronounced in those patients who experienced a CBPDE leading to discontinuation, i.e. those who reached SBP <100 mmHg. Patients who developed CBPDE requiring early discontinuation had lower baseline SBP (131.5 mmHg, n=91), compared to those managed with 50% dose reduction throughout the 48-hour infusion without early discontinuation (161.4 mmHg, n=59); in addition, a higher percentage of these patients were in NYHA class III/IV (65% vs. 48%) with lower left ventricular ejection fraction (LVEF) (34% vs. 44%).

Table 10 Clinical outcomes in serelaxin group of RELAX-AHF with or without CBPDE

Clinical outcome n(%)	**Serelaxin (N=568)**		
CBPDE	**No CBPDE**	**Any CBPDE**	**Discontinuation**
N (%) patients in category[†]	401 (70.6%)	167 (29.4%)	91 (16.0%)
HF/RF rehospitalisations through Day 60 *	38 (9.7)	20 (12.4)	13 (14.9)
All-cause mortality through Day 180	28 (7.0)	13 (7.9)	11 (12.2)

Source: [SCE-Table 3-24]. 'Discontinuation' is a subgroup of 'Any CBPDE'.

The applicant claims that the treatment of patients with SBP >125 mmHg only, combined with the management of SBP decreases in the protocol, has successfully managed the potential risk of hypotension. However, in RELAX-AHF, both baseline SBP < 130 mmHg and CBPDE (SBP < 100 mmHg) are associated with worse outcomes. Low baseline BP is related to the risk of a discontinuation CBPDE. These worse outcomes might be attributable to chance.

Safety in special populations

Most subjects in the pooled Pre-RELAX-AHF and RELAX-AHF trials were elderly (77.5% > 65 years) with 46.5% even older than 75 years. In the elderly patients more AEs were reported

than in younger patients, but in all age groups the incidence of AEs was higher with placebo than in the serelaxin-treated patients. The events 'hypotension' and 'hypokalaemia', that were classified as possible ADR based on >1% higher incidence with serelaxin compared to placebo, occurred more frequently in all age groups, except hypokalaemia in the group ≥ 75 years (Table 11).

The AEs of special interest to older patients were analysed by the Applicant. Older patients have more AEs than younger patients, but this is true for patients treated with both serelaxin and placebo. Some categories in serelaxin-treated patients have a higher incidence of AEs compared to the corresponding placebo group, however this does not preferentially affect the (very) elderly and could easily be attributed to chance. The group >85 years is too small to estimate the risk of AE subgroups accurately.

Table 11 Incidence of AEs by age

Age	<65		65-75		>=75	
	279 (22.5%)		385 (31.0%)		577 (46.5%)	
	s	p	s	p	s	p
Nr of patients (N)	151	128	180	205	279	298
Incidence of AE	43,7%	48,4%	42,8%	50,7%	57,0%	59,7%
blood creat increased*	2,0%	2,3%	1,1%	4,9%	4,3%	4,4%
cardiac failure congestive*	4,0%	7,8%	3,9%	6,3%	3,6%	5,4%
hypotension	1,3%	0,0%	1,1%	0,0%	2,2%	0,3%
hypotension*	0,7%	1,6%	1,7%	2,4%	2,2%	2,0%
hypokalaemia*	7,3%	3,1%	7,8%	5,4%	6,5%	7,7%

Notes: Assessor's table, after SCS 5.1.1.1.3. s = serelaxin 30 µg/kg/day, p = placebo

There are no data in the paediatric population.

The data summarised for safety on renal and hepatic impairment are restricted to PK evaluation, for severe renal impairment even PK data are lacking. The influence of renal or hepatic impairment on PK is limited. It is mentioned in the SmPC that efficacy and safety in these populations have not been studied.

Immunological events

In RELAX AHF, anti-serelaxin antibody analysis was performed in a total of 1122 patients (559 serelaxin, 563 placebo). Anti-serelaxin antibodies were detected in one placebo-treated patient only . The Applicant decided not to analyse the Day 60 samples.

In non-HF studies development of serelaxin antibodies was also assessed. As an example, trial RLXN.C.005 was a randomised controlled Phase II/III Study of serelaxin in Subjects with Systemic Sclerosis with Diffuse Scleroderma. Study drug was administered via continuous SC infusion by a portable pump. In this trial, 40% of patients treated with serelaxin developed antibodies (Table 12). However, the populationand route of administration may have contributed

to this high number. Moreover, the production process of serelaxin in use at the time may not be completely comparable to the current production process.

Table 12 Incidence of anti serelaxin antibody formation in RLXN.C.005 (Scleroderma)

	Placebo	rhRlx 10 µg/kg/day	rhRlx 25 µg/kg/day	rhRlx Combined
Evaluable subjects	95	43	91	134
Incidence of anti-rhRlx antibody formation	3 (3%)	12 (27%)	42 (46%)	54 (40%)
Weeks to seroconversion (range)	4-16	4-24	2-20	2-24

Source: RLXN.C.005 CSR Table 6-16

The screening assays applied in clinical studies (CRLX030A2101, CRLX030A2103, and RELAX-AHF, CRLX030A2201) and RLX.CHF.001 are sufficiently validated and are considered adequate.

According to the guideline on immunogenicity testing (*EMA Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins [EMEA/CHMP/BMWP/14327/2006]*), the sampling schedule for detection of an immune response should be adapted and selected individually for each product, taking into account also its pharmacokinetics. Because serelaxin is used for a single infusion with a maximum of 48 hours, it can be accepted that immunogenicity has been determined by measuring antibodies on a single time point, Day 14 (i.e. 10 days post dose). For most immunogenic events (e.g. vaccination) the antibody response develops fully within 10 days. In cases where the response takes longer, after 10 days the antibody titre is already 50-80% of the maximum response. When looking at the PK, it is clear that the serum serelaxin level is very low again several hours after treatment. Therefore the time of exposure does not lead to a different conclusion with respect to the sampling time for the immunogenicity data. Based on this, the sampling time chosen by the Applicant can be accepted.

If, however, repetitive serelaxin treatments are foreseen, the immunogenicity testing has to be adapted accordingly and additional data will be required.

Safety related to drug-drug interactions and other interactions

From currently available information in the RELAX-AHF study, concomitant medications most commonly used in the standard care of patients with AHF in the hospital or emergency room setting did not appear to alter the PK or safety profile of serelaxin. In addition, serelaxin is unlikely to alter the PK of concomitant medications through direct effects on CYP enzymes, due to the lack of a potential mechanism for direct interaction.

No specific studies evaluating pharmacodynamic interactions for serelaxin and other medicinal products have been performed. The Applicant has presented theoretical considerations leading to the conclusion that the potential for pharmacodynamic interactions is limited. Moreover, PD interactions did not raise concerns during RELAX-AHF. The lack of trials is clearly documented in the SmPC.

Discontinuation due to adverse events

Hypotension and Hypotension* caused 15 discontinuations in the serelaxin 30 µg/kg/day group v 8 in the placebo group (Table 13). The Applicant attributes this to the protocol-specified discontinuation criteria, which are discussed above, as Confirmed Blood Pressure Decrease Event (CBPDE). The Applicant has documented that the vast majority of hypotension events were indeed captured as CBPDE.

Table 13 Incidence of Adverse Events (AEs) Leading to Study Drug Discontinuation From Study Drug Initiation to Day 5 (Population: Safety Set - Pooled RELAX-AHF and Pre-RELAX-AHF)

System Organ Class Preferred Term	Placebo (N=631) n(%)	RLX030 30 µg/kg/day (N=610) n(%)	RLX030 <=30 µg/kg/day (N=650) n(%)	All Serelaxin (N=737) n(%)	Total (N=1368) n(%)
Patients with AE Leading to Study Drug Discontinuation	**25 (4.0)**	**33 (5.4)**	**39 (6.0)**	**51 (6.9)**	**76 (5.6)**
Blood And Lymphatic System Disorders	0 (0.0)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.1)
Hyperchromic Anaemia	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Normochromic Normocytic Anaemia	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Cardiac Disorders	7 (1.1)	3 (0.5)	3 (0.5)	3 (0.4)	10 (0.7)
Acute Coronary Syndrome	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Angina Pectoris*	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Atrial Fibrillation	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Atrial Flutter*	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Atrioventricular Block Second Degree*	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cardiac Failure Acute*	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cardiac Failure Congestive*	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Cardiac Failure*	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Ventricular Fibrillation*	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Gastrointestinal Disorders	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Nausea	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Vomiting	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
General Disorders And Administration Site Conditions	0 (0.0)	3 (0.5)	3 (0.5)	3 (0.4)	3 (0.2)
Chest Pain*	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Fatigue	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Hypothermia	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Immune System Disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Drug Hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Infections And Infestations	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Urinary Tract Infection	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Investigations	2 (0.3)	1 (0.2)	1 (0.2)	1 (0.1)	3 (0.2)
Blood Pressure Decreased	2 (0.3)	1 (0.2)	1 (0.2)	1 (0.1)	3 (0.2)
Nervous System Disorders	5 (0.8)	5 (0.8)	5 (0.8)	5 (0.7)	10 (0.7)
Cerebrovascular Accident	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Dizziness	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	4 (0.3)
Embolic Stroke	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Headache	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.1)	2 (0.1)
Hypotonia	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Somnolence	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Psychiatric Disorders	0 (0.0)	4 (0.7)	4 (0.6)	4 (0.5)	4 (0.3)
Anxiety	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Confusional State	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Delirium	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)

Mental Disorder Due To A General Medical Condition	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Renal And Urinary Disorders	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Oliguria	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Respiratory, Thoracic And Mediastinal Disorders	2 (0.3)	2 (0.3)	2 (0.3)	3 (0.4)	5 (0.4)
Acute Pulmonary Oedema*	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.1)	2 (0.1)
Acute Respiratory Failure*	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Haemoptysis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Respiratory Failure*	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Skin And Subcutaneous Tissue Disorders	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.1)	2 (0.1)
Hyperhidrosis	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.1)	2 (0.1)
Vascular Disorders	9 (1.4)	15 (2.5)	21 (3.2)	31 (4.2)	40 (2.9)
Hot Flush	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hypotension	0 (0.0)	8 (1.3)	8 (1.2)	8 (1.1)	8 (0.6)
Hypotension*	8 (1.3)	7 (1.1)	13 (2.0)	23 (3.1)	31 (2.3)

* Disease-related event (DRE). The incidence across the two hypotension terms cannot be summed since a patient may have experienced an event in either category at different times during the study.
Note: At each level of summation (System Organ Class (SOC) and Preferred Term), patients are counted once per SOC and preferred term.
Note: Incident AEs are considered those AEs with an onset date and time after the initiation of study drug.
Note: 'Patients With at Least One AE' counts every patient, who experienced an AE episode in this interval.
Source: [SCS-Appendix 1-Table 14.3.1-8]

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

The evaluation of safety is based on the pooled safety populations of Pre-RELAX-AHF and RELAX-AHF, and describes 737 AHF patients who received serelaxin and 631 patients who received placebo. Data from the older ('legacy') trials suffer from differences in design, dose, route of administration and manufacturing processes and are considered supportive only. The EMA scientific advice (EMA/CHMP/SAWP/784780/2010) considered that the size of the database might be sufficient, in relation to the benefits that would be demonstrated.

Approximately 50% of the patients in the serelaxin groups experienced at least one AE with a slightly lower percentage compared to the placebo group, driven by the incidence of cardiac disorders. Hypokalaemia* (serelaxin: 7.1% placebo: 6.0%) and hypotension (1.6% in serelaxin 30 µg/kg/day, and 0.2% in placebo) were the only AEs reported by ≥1% more patients in the serelaxin group compared to the placebo group. These events were identified as potential ADRs for serelaxin. The methods of the Applicant's AE analysis were acceptable. Hypokalaemia was proposed to be followed as a potential risk in the EU RMP.

A higher percentage of patients in the serelaxin group (92 patients, 15.1%) compared to the placebo group (82 patients, 13.0%) reported at least one SAE from study drug initiation to Day 14. Between 14 and 60 days, only hospitalisations were captured (see secondary efficacy endpoint).

Hypotension is an identified risk of serelaxin and was also the most important AE leading to discontinuation. In the AHF trials, measures were included in the protocol to mitigate this risk, including baseline SBP > 125 mmHg, dose reduction if BP dropped by >40 mmHg and treatment discontinuation if BP <100 mmHg. This occurred in more patients on serelaxin (29.4%) compared to placebo (18.1%) and resulted in dose reduction (44.9% vs. 41.7%), discontinuation (64.1% vs. 68.9%) or a dose reduction followed by a discontinuation (9.6% vs. 11.7%). These

BP events were associated with few or no symptoms in most patients. Following dosing adjustment, there was partial recovery of the SBP during the first 60 minutes by approximately 10 mmHg, somewhat less in the placebo group. Five hours following event onset, the mean SBP reduction was 31.9 mmHg (from 47.8 mmHg at event onset) after dose reduction and 25.1 mmHg (from 41.7 mmHg at event onset) after discontinuation.

AEs indicative of renal impairment were reported by a lower percentage of patients in the serelaxin group (5.9%) compared to the placebo group (9.2%) to Day 14. Smaller percentages of patients had serum creatinine increases at any post-baseline visit in the serelaxin group. Also hepatic events (commonly caused by congestion in these patients) were reported by a lower percentage of patients in the serelaxin group (0.8%) compared to the placebo group (2.5%).

Death (due to all causes by Day 180), occurred less in the serelaxin group (44 patients, K-M estimate 7.4%) compared to the placebo group (72 patients, K-M estimate 11.7%; hazard ratio (HR) = 0.61, 95% CI: 0.42, 0.89, p=0.0110) (Figure 10). This analysis is consistent in subgroups, except in the group with baseline SBP between 125 and 130 mmHg (HR 1.04), and the group with baseline eGFR ≥ 60 mL/min/m² (HR: 1.51), which may be a chance finding The analysis of deaths adjudicated to CV causes (84% of deaths, HR = 0.63) is also consistent. The most commonly reported CV causes of death were heart failure/pump failure (3.6% in serelaxin and 3.1% in placebo) and sudden death (3.0% in the placebo group vs. 1.5% in the serelaxin group). Also non-CV deaths favoured serelaxin (7 vs. 10).

It is not easy to link the primary pharmacology of serelaxin (as demonstrated in humans) to this potential mortality benefit. A similar benefit has not been shown for other vasodilatators like nitrates. Exploratory analyses presented in the dossier have linked the mortality finding to prevention of WHF, worsening renal failure and to biomarkers related to organ damage (Heart – troponin-T, Kidney – Cystatin-C) and congestion (NT-pro-BNP).

No major laboratory findings were noted. Higher proportions of patients in the serelaxin group compared to the placebo group reported >20% decrease from baseline to Day 14 for haemoglobin (9 patients, 1.5% vs. 4 patients, 0.6%, respectively), haematocrit and red blood cells. This is a potential risk in the RMP based on 'legacy' trials. No adverse effects indicating arrhythmogenic or QT prolonging properties of serelaxin have been observed in clinical trials. In the database, no differences were observed in AEs related to cardiac arrhythmias. No apparent changes were noted in ECG results, although only a very small number of patients were specially investigated. There were no clinically significant effects on heart rate in the RELAX trials. No significant differences were detected in pulse, respiratory rate, body temperature or weight. In RELAX-AHF, median change from baseline in weight was similar in the serelaxin and placebo groups (Day 3: serelaxin = placebo = -2.0 kg).

Most subjects in the RELAX-AHF trials were elderly (77.5% > 65 years) with 46.5% even older than 75 years. In the elderly patients more AEs were reported than in younger patients, but in all age groups the incidence of AEs was higher with placebo than in the serelaxin-treated patients.

In RELAX AHF, anti-serelaxin antibody analysis was performed on Day 14. Anti-serelaxin antibodies were detected in one placebo-treated patient only. The CHMP concluded that for this application immunogenicity poses no serious problem, but for repeat administration immunogenicity must be reassessed.

In the RELAX-AHF study, routine concomitant medications apparently did not alter the PK or safety profile of serelaxin. No specific studies evaluating pharmacodynamic interactions for serelaxin have been performed.

2.6.2. Conclusions on the clinical safety

Serelaxin has a benign safety profile. In the RELAX trial, AEs and mortality, but not hospitalisations favoured serelaxin. Hypotension and hypokalaemia are the most frequently occurring AEs, but they appear manageable when the right precautions are taken.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system Master File included in Module 1.8.1 of the submitted dossier fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

Based on the PRAC review of the Risk Management Plan version 1.2, the PRAC considers by consensus that the risk management system for serelaxin is acceptable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 14 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	- Hypotension
Important potential risks	- Hemoglobin/hematocrit transient decrease - Hypokalemia
Missing information	- Repeat use of serelaxin continuous IV infusion for up to 48 hours (including immunogenicity) - Patients with severe renal impairment (GFR <30 mL/min /1.73 m2) - Use in patients with relevant co-morbidities: • Cardiac diseases: Left-ventricular outflow

Summary of safety concerns	
	obstruction physiology (e.g. severe valvular aortic stenosis, obstructive cardiomyopathy), severe aortic regurgitation, severe mitral stenosis, acute myocarditis, cardiomyopathy (hypertrophic, restrictive or constrictive), recent acute coronary syndrome or significant arrhythmias (ventricular tachycardia, bradycardia <45 bpm, second/third degree AV block, atrial fibrillation/flutter with a ventricular response rate of >120 bpm), severe heart failure requiring mechanical support (e.g. intra-aortic balloon pump, endotracheal intubation, mechanical ventilation, or any ventricular assist device), low cardiac output or systolic blood pressure below 110 mmHg; • Severe cerebrovascular events: Recent events such as stroke; • Concomitant diseases: Active infection, fever, pulmonary disease, non-cardiac pulmonary oedema, or organ transplant. - Use in pregnant and breast-feeding women - Use in non-Caucasian patients - Use in paediatric patients <18 years

The PRAC agreed.

Pharmacovigilance plans

Table 15: Ongoing and planned studies in the PhV development plan

Activity/Study title (category 1-3)*	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Phase 3, outcome study (CRLX030A2301) Interventional Category 3	Assess frequency, safety, tolerability and outcome, in case a patient experiences a BP decrease event. Monitor compliance with study protocol mandated study drug dose reduction	Hypotension	started	Q4 2016

Activity/Study title (category 1-3)*	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
	and discontinuation. Assess frequency, safety, tolerability and outcome, in case a patient experiences a transient decrease in hemoglobin/hematocrit or any associated AE. Assess frequency, safety, tolerability and outcome, in case a patient experiences serum potassium decrease or any associated AE indicative of Hypokalemia. Proposed activity aims to collect data in non-Caucasian patients exposed to serelaxin, in case this become available, and evaluate safety, tolerability and efficacy.	Hemoglobin/ hematocrit transient decrease Hypokalemia Use in non-Caucasian patients		
Phase 2, repeat dose study CRLX030A2209 Interventional Category 3	Proposed activity aims to collect data on repeat use of serelaxin continuous IV infusion for up to 48 hours and evaluate safety, tolerability and efficacy. In particular, the repeat dose study will evaluate potential anti-serelaxin Ab formation and AEs indicative of hypersensitivity reactions/immune disorders after single and	Repeat use of serelaxin continuous IV infusion for up to 48 hours (including immunogenicity)	planned	Q3 2016

Activity/Study title (category 1-3)*	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
	repeat dosing and assess safety and tolerability.			
Phase 1, renal impairment PK study CRLX030A2102 Interventional Category 3	Renal impairment PK study will investigate the pharmacokinetics and safety of serelaxin in subjects with severe renal impairment (eGFR <30 mL/min/1.73 m2, not requiring dialysis) and matched controls.	Use in patients with severe renal impairment (GFR <30 mL/min /1.73 m2)	started	Q3 2014
PIP (EMEA 001168-PIP01-11-M01): • Phase 2 study CRLX030A2208 • Phase 3 study CRLX030A2303/ CRLX030A2303E 1 Interventional	The pediatric program is designed to evaluate the use of serelaxin for the treatment of pediatric patients from birth to <18 years with AHF following surgical repair of a congenital heart defect.	Use in pediatric patients <18 years	planned	Q1 2021

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 16: Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Hypotension	Labelling in SmPC/PIL	None
Haemoglobin/ haematocrit transient decrease	Labelling in SmPC/PIL	None
Medication error	Labelling in SmPC/PIL	None

Microbial Contamination	Labelling in SmPC/PIL	None
Repeat use of serelaxin continuous IV infusion for up to 48 hours (including immunogenicity)	Labelling in SmPC/PIL	None
Use in non-Caucasian patients	Labelling in SmPC/PIL	None
Use in patients with severe renal impairment (GFR <30 mL/min /1.73 m_2**)**	Labelling in SmPC/PIL	None

The PRAC, having considered the data submitted, was of the opinion that the proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Relaxin is a naturally occurring heterodimeric peptide hormone (containing a 24 amino acid A-chain and a 29 amino acid B-chain); serelaxin is human recombinant relaxin. Relaxin has a physiologic role during pregnancy to facilitate the adaptation of the body to the different circulation of pregnancy. A Marketing Authorisation is sought for the treatment of acute heart failure (AHF) in patients with systolic blood pressure above 125 mmHg.

Pharmacodynamic effects of serelaxin in the vasculature are initiated upon binding to its G-protein coupled relaxin/insulin-like family peptide receptor 1 (RXFP1) and trigger the activation of the endothelial endothelin type B (ETB) receptor and nitric oxide (NO) synthase. The NO mediated vaso-relaxation results in a reduction of Pulmonary Capillary Wedge Pressure (PCWP), mean Pulmonary Arterial Pressure (PAP) and systemic Blood Pressure (BP). These changes are confirmed in a haemodynamic study in patients with AHF using the proposed dose as 20 hours IV infusion (Study CRLX030A2201). In this trial no change in Cardiac Index was found. Serelaxin has been shown to increase Renal Blood Flow (RBF) but not Glomerular Filtration Rate (GFR) in Study CRLX030A2202, a placebo-controlled study investigating the renal haemodynamic effects

of serelaxin at the proposed dose rate as IV infusion for 24 hours compared to placebo in patients with chronic heart failure (CHF).

The efficacy dossier consists of one pivotal study RELAX-AHF (RLX.CHF.003). This was a Phase III, randomised, double-blind, study with patients receiving a continuous intravenous (IV) infusion of placebo or serelaxin (nominally 30 µg/kg/day) for up to 48 hours, in a randomised ratio of 1:1. Patients in both treatment groups also received standard therapy for AHF. Eligible patients were hospitalised for AHF and had required ≥40 mg IV furosemide since presentation. Entry criteria further required stable systolic blood pressure >125 mmHg and impaired renal function (eGFR between 30-75 mL/min/1.73 m²). In general the AHF observed in the trial population was not particularly severe or acute. In contrast to other HF trials, subjects with SBP < 125 mmHg were excluded, which is consistent with the BP lowering effects of serelaxin. A total of 1161 patients were randomised to the study RELAX-AHF. Vital status at Day 180 was not available for only 14 (1.2%) patients indicating adequate follow-up. Baseline characteristics were well balanced between groups.

The first co-primary endpoint was sustained relief of dyspnoea, measured by the AUC (area under curve) representing the change in patient-reported dyspnoea from baseline measured by 100-mm VAS (Visual Analog Scale) through Day 5. This endpoint is acceptable in the *EMA Guideline on the development of medicinal products for the treatment of AHF (CPMP/EWP/2986/03)*, although 30-day all-cause mortality is preferred. The results were 2756 mm-hours and 2308 mm-hours in the serelaxin and placebo groups, respectively. The mean difference in VAS AUC between treatment groups was 447.7 mm-hours (95% CI 120.0, 775.4; t-test p=0.0075; Wilcoxon rank-sum test p=0.0819). The study was considered to have met the primary objective of demonstrating efficacy of serelaxin in dyspnoea relief if either co-primary endpoint was statistically significant at the two-sided 0.025 level, or if both tests were significant at the two-sided 0.05 level (Hochberg procedure). With these results, the study met this primary objective.

There were two dose-response studies carried out. In the Phase 1 study (RLX.CHF.001), 16 patients were treated with escalating doses (10-960 µg/kg/day) to establish a dose range to be tested. The Phase II study (Pre-RELAX-AHF, n=234), study evaluated 4 doses of serelaxin (10, 30, 100, and 250 µg/kg/day) vs. Placebo. The 30 µg/kg/day dose level showed a statistically significant positive result on the primary outcome (dyspnoea by Likert scale to 24 hours) and was selected for further development. Higher doses were not consistently more effective and the trial failed to identify a dose-response relationship.

In the RELAX-AHF trial, most participants were elderly subjects. The clinical study report provides data for the following age groups: <65, ≥65, <75 and ≥75 years. The efficacy results in the elderly populations are similar to the younger populations. As serelaxin is not metabolised and intrinsic factors like age, gender and race do not affect the pharmacokinetics of serelaxin, the product can be safely used from a pharmacokinetic point of view in such special populations.

Uncertainty in the knowledge about the beneficial effects.

In RELAX-AHF the comparator was inactive placebo and the protocol did not strictly prescribe the use of vasodilatators (nitrates) in the control arm. This produced post-randomisation heterogeneities between the study arms, most importantly a difference in arterial pressure throughout the infusion period of serelaxin (change from baseline systolic blood pressure at 9

hours serelaxin 15.9 mmHg (95%CI: 14.5-17.3) and placebo 10.1 mmHg (95%CI: 8.6-11.6). Arterial pressure is a main component of cardiac afterload, a determinant of heart work and a key target for therapy. Because the study protocol did not lead to a reasonable use of i.v. nitroglycerine (no difference compared to serelaxin group) while the vasodilatator effect of serelaxin resulted in the above mentioned difference in arterial pressure and heart workload, the placebo arm was undertreated during the study-drug infusion phase compared to the active arm. This casts doubts on the validity of the trial and its outcomes.

The validity and clinical relevance of the findings regarding improvement in dyspnoea were seriously questioned (major objection). VAS measurements for the primary analysis were imputed in patients who had died or met the criteria for the outcome Worsening Heart Failure (WHF) during the measurement period: the worst score observed in any patient at any time-point was carried forward for all time-points after the time of onset of the event, regardless of whether the score was missing or not. Thus, despite there were additional measurements available after an event of WHF, the imputed values were used instead. This is an unusual approach; the measured values should be included in the analysis (irrespective of whether WHF occurred or not) and in case of truly missing values multiple imputation is the preferred method (and not the imputation by the worst value or baseline value as the Applicant did). In RELAX-AHF the results were driven by the values that were imputed after the subject was classified as having an event of WHF. The impact of these imputed values was assessed by sensitivity analyses. One of these employed only observed data. The mean AUC was 2908 mm-hr for the placebo group and 3034 mm-hr for the serelaxin group, resulting in a difference of 126 mm-hr (95% CI: -128,381; p = 0.33 by t-test). This corresponds to a mean improvement of only 1.1 mm, with the 95% CI including zero difference.

The clinical relevance of the AUC of VAS change from baseline as reported was questioned. The AUC-difference that was considered clinically relevant for the sample size calculation was based on an experts' opinion and was not achieved during the study. The sample size was adequate to detect a minimally clinically meaningful treatment difference of 468 mm-hour (4 mm difference across time points on average). Compared to a mean improvement in VAS of 25 mm in the placebo group, the clinical relevance of this 4 mm difference seems rather limited. The value observed corresponds to a mean improvement of 3.8 mm.

In addition, the positive results on dyspnoea measured by VAS AUC were not confirmed by a similar effect on the co-primary endpoint measured by the Likert scale. Apart from the effect on the dyspnoea, the results pertaining to the secondary endpoints, including effects on cardiovascular morbidity by measuring 'Days alive and out of hospital' through Day 60 and CV death or rehospitalisation through Day 60 are not supportive of a beneficial treatment effect.

A very large number of exploratory efficacy endpoints were investigated. All-cause mortality was assessed as a safety measure at various time points. A lower percentage of patients in the serelaxin dose group 30 µg/kg/day (44 patients, K-M estimate 7.4%) compared to the placebo group (72 patients, K-M estimate 11.7%) died due to all causes through Day 180 (hazard ratio (HR) = 0.61, 95% CI: 0.42, 0.89, p=0.0110). Most (84%) deaths were cardiovascular; the HR for the risk of cardiovascular deaths was similar (0.63, 95% CI 0.43, 0.93). The reason for this difference remains unexplained. It could be a chance finding, certainly in view of the limited effects shown on other secondary outcomes. However, the haemodynamic findings seem favourable and could contribute to prognostic improvement. Other beneficial effects may be

derived from less WHF as assessed by the physicians (6.5% vs. 12%) and less use of furosemide (161 vs. 213 mg) but are difficult to interpret. The biomarkers that were studied, hs-cTnT, Cystatin C and NT-proBNP, all show favourable changes in serelaxin patients compared to placebo that were related to improved survival at Day 180, but their implications remain uncertain.

Consistent with clinical practice, the large majority of participants had 'acute worsening of chronic heart failure', leading to limited data on other types of patients with AHF; however the data are likely representative of the entire target population. As confirmed by the Applicant and by investigator during the GCP inspection, patients were considered for inclusion only after routine evaluations had confirmed their (potential) eligibility. This reduces the risk of selection bias. Efficacy trials in the special populations of severe renal impairment and hepatic impairment were not performed. A paediatric investigation plan was agreed, but no results of the studies agreed therein are available.

Further concerns have arisen from the number of Amendments dealing with major aspects of the study conduct (#3 that increased sample size) and endpoint adjudication (#5 defining the endpoint "worsening heart failure"). Both Amendments were introduced in a late phase after study initiation. However, after clarifications by the Applicant, the CHMP agreed that these amendments do not jeopardise the interpretation of the trial.

As stated above, the two dose-response studies failed to identify a dose-response relationship and higher doses were not consistently more effective. The dose-response curves for the pharmacological effects of serelaxin may well be U-shaped, further complicating the characterisation of the dose-effect relations. The large number of endpoints explored and wide margin for 'favourable trend' ($p < 0.20$) in the Phase II trial carry the risk of chance findings.

Risks

Unfavourable effects

The primary dataset used for the evaluation of safety is the pooled safety population of Pre-RELAX-AHF and RELAX-AHF, consisting of all patients who received at least one dose of trial medication. This population consists of 737 AHF patients who received serelaxin and 631 patients who received placebo.

The number of AEs was slightly smaller in the serelaxin group compared to placebo. Two AEs were noted that occur ≥1% more frequently with serelaxin: 'hypotension' and 'hypokalaemia'. Hypotension is clearly related to the vasodilatatory effect of serelaxin and was included as identified risk in the RMP for this product. It is not accompanied by an increase in heart rate. An SBP of at least 125 mmHg was required for inclusion in the trials. The trial protocol further included criteria to reduce the dose (if SBP had decreased by 40 mmHg compared to baseline) or discontinue treatment (if SBP decreased below 100 mmHg). These criteria applied in 167/568 (29.4%) of the patients in the serelaxin group of RELAX-AHF and 103/570 (18.1%) of placebo patients in the same trial. These forced dose reductions were termed 'Confirmed Blood Pressure Decrease Events' (CBPDE) in this dossier. The vast majority of hypotensive events were captured as CBPDE. Hypotension was also the most frequent AE leading to discontinuation of the trial. Hypokalaemia was captured as an AE in 7.1% of patients in the serelaxin 30 µg/kg/day group and 6.0% in the placebo group. This finding is not confirmed by a change in mean serum

potassium, although the PD trial showed a small difference in potassium excretion. The Applicant has not been able to link hypokalaemia to the mechanism of action of serelaxin and concomitant medications are known to influence serum potassium levels. Hypokalemia was included as a potential risk in the RMP and should be followed up in future trials. Because of the effects of concomitant medications, serum potassium levels should be monitored in clinical practice irrespective of serelaxin use.

The number of patients who experienced at least one SAE was higher in the serelaxin group (92 patients, 15.1%) compared to the placebo group (82 patients, 13.0%). There was no clear pattern in these SAEs, as 'Respiratory, Thoracic and Mediastinal Disorders' was the only SOC that occurred ≥1% more frequently in the serelaxin group (placebo 6/631 (1.0%) vs. serelaxin 13/610 (2.1%)); cardiac SAEs were slightly less frequent with serelaxin than with placebo.

Most subjects in the RELAX-AHF trials were elderly (>65 years: 77.5%) with 46.5% even older than 75 years. The analysis of AEs, SAEs and mortality is consistent over age groups.

Uncertainty in the knowledge about the unfavourable effects

The safety database consists of 1431 AHF serelaxin-treated patients, 737 of which were treated with IV serelaxin at the proposed regimen and 410 received the full dose, which are rather small numbers, especially in a common disorder like AHF.

In the pooled RELAX-AHF and Pre-RELAX-AHF studies, higher proportions of patients in the serelaxin group compared to the placebo group reported >20% decrease from baseline to Day 14 for haemoglobin (9 patients, 1.5% vs. 4 patients, 0.6%, respectively), haematocrit (10 patients, 1.6% vs. 4 patients, 0.6%, respectively) and red blood cells (RBC) (7 patients, 1.1% vs. 4 patients, 0.6%, respectively. The applicant attributed these changes to haemodilution, which would be consistent with the vasodilation caused by serelaxin. However, the 25% increase in plasma volume after initiation of treatment for AHF required to explain a 20% drop haemoglobin seems not realistic. The Applicant agreed that a potential contribution of serelaxin to haemodilution cannot be excluded based on the available data. Moreover, currently a modest antidiuretic effect cannot be excluded. The SAG members confirmed that this issue is not well understood. The issues of "Hemoglobin/hematocrit transient decrease" was included as important potential risks in the proposed RMP.

Although there are no signals concerning ECG changes or arrhythmias from the safety database or from preclinical studies, systematic ECG analysis has only been performed in very few patients; a designated substudy of the RELAX-AHF trial included only 22 patients.

The data summarised for safety on renal and hepatic impairment are restricted to PK evaluation. The influence of renal or hepatic impairment on PK is limited. Given that no outcome data for efficacy and safety in these populations were presented, this information was reflected in the proposed SmPC.

Usual medications in AHF are not likely to exhibit pharmacokinetic interactions with serelaxin, based on its properties as an endogenous hormone and lack of effects on cytochrome P (CYP) enzymes. However, no specific studies evaluating pharmacodynamic interactions for serelaxin and other products have been performed. The potential for pharmacodynamic interactions is low on theoretical grounds and the experience in RELAX-AHF.

The immunologic risk of repeat administration of serelaxin in AHF cannot be assessed because of the lack of data, therefore repeated administration cannot be recommended currently.

Benefit-risk balance

The benefit of serelaxin in terms of improvement of dyspnoea and improved survival has not been conclusively demonstrated due to methodological issues and questionable clinical relevance.

Importance of favourable and unfavourable effects

The treatment focus in AHF may include rapid relief of congestion, improvement in haemodynamic status, correction of the underlying cause and reduction in mortality. According to the EMA *Guidance on clinical investigations of medicinal products for the treatment of cardiac failure/Addendum on acute heart failure (CPMP/EWP/2986/03)*, reduction in mortality is the preferred primary endpoint, but provided that a deleterious effect on mortality is ruled out, improvement of symptoms and correlation of haemodynamic improvement with clinical findings can be accepted as evidence of efficacy. Based on the RELAX-AHF trial, a deleterious effect of serelaxin on mortality is unlikely; however, any beneficial effect on mortality needs to be confirmed by a separate clinical trial. In the pharmacodynamic trials submitted with the responses to the Day 12O List of Questions, the Applicant has shown that haemodynamic improvements as an objective measure of clinical efficacy are observed.

Relief of dyspnoea was assessed for both short-term relief (6-24 h), and for persistent relief (0-5 Days). A significant effect was observed for the latter using the VAS-scale but not on the former using the Likert-scale. The VAS results turn out to be driven by imputations which were applied after rescue therapy had become necessary (termed 'worsening heart failure' or WHF). This WHF may be important in itself (see below), but the imputed values are not reflective of the dyspnoea of the patients. Moreover, the clinical relevance of the effect size was questioned.

Both all-cause and cardiovascular (CV) mortality were assessed as exploratory endpoints on Day 30, 60 and 180. All-cause mortality showed a potential benefit (Hazard ratio: 0.63; 95% CI (0.43, 0.91), p=0.013) that even tested statistically significant at 180 days. Also reassuring in terms of safety, these exploratory results should be considered as hypothesis-generating and warrant further confirmation, in particular as re-hospitalisations were in favour of placebo and the secondary endpoint 'Days Alive and Out Of Hospital' (capturing mortality, index-hospitalisation and re-hospitalisations) at Day 60 showed a neutral result. The suggested mechanism of action (prevention of organ damage) needs further clarification, in particular the effects observed on the biomarkers such as troponins and cystatin C.

The treating physicians had a more favourable opinion about the status of the serelaxin-treated patients than about placebo patients. This is evident from exploratory variables rating physical examination over time, length of hospital stay, use of IV diuretics and occurrence of WHF. However, these findings are not measures of patient well-being or validated surrogates for survival.

The safety profile of serelaxin is benign, although there are some uncertainties. The database size is limited but can be accepted as discussed in the EMA scientific advice. Re-hospitalisations were higher with serelaxin but mortality plus re-hospitalisations were roughly in line for both groups. Pharmacodynamic drug-drug interactions have not been studied specifically, although

serelaxin was investigated on top of standard of care. Management of hypotension did not result in many adverse events (AEs). Hypokalaemia may or may not be an adverse drug reaction (ADR) of serelaxin, but potassium will be routinely followed in these patients anyway. Even though not directly relevant for this assessment, the concern was raised that repeat administration and immunogenicity could pose a problem later. Fractures and promotion of cancer are rare (if at all existent) and seem unlikely ADRs after use for only 48 hours.

Benefit-risk balance

Discussion on the benefit-risk balance

In general, this Application was considered by the CHMP to be premature and major questions remain with regard to the clinical relevance of the findings presented in current application, the methodology used and the background medication. Only one single pivotal trial has been submitted and, in accordance with the *EMA Points to Consider on application with (1) Metaanalyses (2) One pivotal study (CPMP/EWP/2330/99)* such a submission has to show at least statistically compelling and clinically relevant results. In this dossier these conditions are not met and confirmatory data are needed to support evidence of clinical benefit.

In their responses to the Day 180 List of Outstanding Issues, the Applicant has provided further information about WHF as it was observed in RELAX. Although most (88%) WHF events were treated with an increase of IV diuretics, there were also 178 patients in whom the diuretic dose was doubled without WHF being defined as an endpoint.

A scientific advisory group (SAG) was convened to further discuss the clinical relevance of the findings in terms of clinical relevance of the findings in the study, the used methodology and background therapy. The SAG concluded that a 4 mm reduction in VAS seems to be a very small improvement and unlikely to be clinically relevant, especially when most patients used 5 mm increments in the VAS to mark their dyspnoea status as it has been applied in scaled design. To impute the value of zero when WHF has occurred seems to be a too extreme approach and carrying it beyond the time of WHF for the rest of the measurement points too strict. The Likert scale results are in line with the VAS results when the VAS values are not imputed. The SAG experts did not consider possible to value 'clinical worsening' *per se* in terms of dyspnoea. These entities are too different to be combined in a single measure. The SAG commented that the VAS is clearly patient-reported, but the classification of WHF is a (subjective) physician decision. Therefore, the endpoint has characteristics of a composite endpoint. The attempt to combine these measurements by imputations after WHF is considered not robust. Thus, the Applicant has still failed to relate a mean improvement on the dyspnoea VAS scale to a relevant decrease in the patient's feeling of dyspnoea. Instead, in the responses to Day 18o List of Outstanding Issues, the Applicant has shifted focus from the relevance of the VAS score to the relevance of WHF, far beyond what was predefined.

The definition of WHF is not yet universally agreed and it is currently not considered a parameter that can be used as a surrogate endpoint to study effects of medicinal products on cardiovascular outcome. A future role of this parameter, e.g. in guidelines, would need to be discussed further. The SAG commented that the definition criteria used in RELAX do not account for the underlying reason, i.e. do not take into account ventricular rate, occurrence of atrial fibrillation, peripheral oedema or infections like the occurrence of pneumonia, which makes the interpretation difficult.

With respect to mortality, the SAG noted that the observed difference in the mortality endpoint at 6 months lacks a pathophysiological explanation given only a short term administration of the drug. It was an exploratory parameter and the study was not powered for measuring mortality as an efficacy endpoint. It was rather used as a safety parameter. The result was largely driven by CV mortality; however it has not been shown that a difference in the pump failure related events contributed to a relevant extent. Stroke (placebo: 8 events, serelaxin: 1 event) contributed significantly to the overall difference. The increase in the mortality difference over time cannot be explained on the basis of the biological activity of the compound, as known so far. Thus, it might be of added value to study this parameter in a properly designed prospective trial.

According to the SAG, the overall haemodynamic findings including effect on filling pressures are in line with decongestion. The lack of cardiac index (CI) increase was discussed and not felt to be a matter of major clinical concern, however it was not clearly understood given the reduction in systemic vascular resistance. The observed haemodynamic response lacks a dose response relationship explanation in the data provided so far and thus dose adjustment would be difficult if not impossible in clinical practice.

Only a small cohort of the study population was given nitrates as part of the background therapy, which was lower than the SAG members would have expected based on the available usage data (e.g. Euro Heart Survey) and common practice. The reason is probably partly investigators and partly protocol-driven (iv. nitrates in patients with SBP below 150 mm Hg were not allowed). It is not clear to which extent and in which direction the low use of nitrates might have affected the results.

Repeat administration has not been studied but raises issues about immunogenicity and consequently pharmacokinetic changes and possibly hypersensitivity reactions. In this population the indication for repeat administration will certainly arise. A clinical trial, as proposed in the RMP, would be necessary.

It is agreed with the Applicant, based on theoretical considerations, that the risk of unexpected interactions between serelaxin and other drugs commonly used in heart failure is low. The Applicant has initiated a large outcome trial to further define the clinical role of serelaxin.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Reasanz in the proposed indication of:

"the symptomatic treatment of acute heart failure in adults with normal to elevated blood pressure systolic blood pressure above 125 mmHg. It should be used on top of standard of care, including loop diuretics"

the CHMP considers by consensus that the efficacy of the above mentioned medicinal product is not sufficiently demonstrated. In accordance with Article 12(1) of the Regulation 726/2004 the CHMP therefore recommends the refusal of the granting of the Marketing Authorisation for the

above mentioned medicinal product.

This is based on the following grounds:

- **Clinical relevance.** The Applicant has failed to relate a mean improvement on the dyspnoea Visual Analogue Scale (VAS) scale to a relevant decrease in the patient's feeling of dyspnoea.

- **Used methodology.** The estimate of the effect size is not robust. The results were driven by the imputations that were applied for non-missing data after event of Worsening Heart Failure (WHF) with a large difference between the estimate according to the protocol and a conservative intention-to-treat approach based on observed values. Worsening Heart Failure cannot robustly be combined with the Visual Analogue Scale area under curve (VAS AUC) results and its use as an endpoint needs further justification.

- **Background therapy.** In the trial, the use of i.v. nitrates in the placebo arm was lower than expected based on current guidelines. Nitrates, similar to serelaxin, have vasodilating properties contributing to their therapeutic effect. Thus, this undertreatment with nitrates in the placebo arm may have well contributed to the observed difference in afterload compared with seralaxin during the period in which the primary end point was assessed, potentially affecting the size of the outcome measurement.

For an application based on a single pivotal trial in acute heart failure, the effect was not sufficiently demonstrated and the pre-defined level of clinical significance was not met. Therefore further confirmation is needed.

For these reasons, the benefit/risk of serelaxin in the proposed indication:

"*symptomatic treatment of acute heart failure in adults with normal to elevated blood pressure systolic blood pressure above 125 mmHg. It should be used on top of standard of care, including loop diuretics*" is considered as negative.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and follow-up measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Furthermore, the CHMP, in light of the negative recommendation, is of the opinion that it is not appropriate to conclude on the new active substance status at this time.

5. Re-examination of the CHMP opinion of 23 January 2014

Following the CHMP conclusion that Reasanz (serelaxin) was not approvable in the proposed indication:
"*symptomatic treatment of acute heart failure in adults with normal to elevated blood pressure systolic blood pressure above 125 mmHg. It should be used on top of standard of care, including loop diuretics*",

because for an application based on a single pivotal trial in acute heart failure, the effect was not sufficiently demonstrated and the pre-defined level of clinical significance was not met,
the applicant submitted detailed grounds for the reexamination of the grounds for refusal.

5.1 Detailed grounds for re-examination submitted by the applicant

The applicant provided with the grounds for re-examination a revised Summary of Product Characteristics (SmPC), including the modified proposed indication:

Reasanz is indicated for the treatment of acute heart failure in adults with systolic blood pressure above 125 mm Hg. It should be used on top of standard of care, including loop diuretics.

The applicant presented in their submission the following grounds for re-examination:

Ground 1a

Clinical relevance. The Applicant has failed to relate a mean improvement on the dyspnoea Visual Analogue Scale (VAS) scale to a relevant decrease in the patient's feeling of dyspnoea.

Summary of the Applicant's response

The RELAX-AHF study met its primary objective with serelaxin demonstrating a 19.4 % improvement on the dyspnea visual analog scale (VAS) area under the curve (AUC) endpoint through Day 5 versus placebo on top of standard of care (SoC). This effect is highly significant with a p-value of 0.0075 and consistent in all demographic and clinical subgroups. This result reflects mild improvement in the patients' shortness of breath and includes the clinically important 47 % reduction of worsening heart failure (WHF) episodes. Of note, this was observed following approximately 8 hours of SoC treatment before randomization and also in the context of lower diuretic use in the serelaxin group.

Importantly, the VAS AUC primary endpoint was designed as a multicomponent endpoint that captured 1) change in dyspnea score, 2) occurrence of in-hospital WHF and 3) death, making it sensitive to the entire range of patients' treatment responses. WHF represents a deterioration of the patient's clinical condition and consequently a treatment failure. This potentially life threatening event profoundly alters the patient's subsequent clinical course. This is evidenced by

a significant association of WHF with prolonged use of IV diuretic therapy, changes indicating a worsening in the status of cardiovascular and renal biomarkers including troponin T, longer length of stay (LoS) and increased mortality. Overall the effect of serelaxin on the primary VAS AUC endpoint therefore indicates an important and clinically relevant improvement of the clinical course of the patient by reducing these important clinical events and improving prognosis beyond current SoC. Serelaxin is the first agent to do so without adversely effecting mortality.

In addition, the robustness of the findings on the VAS AUC primary endpoint in RELAX-AHF is supported by:

- Significantly shorter time to moderate or marked dyspnea improvement using the Likert scale and consistency with VAS AUC results in an additional analysis of the Likert primary endpoint when accounting for both improvement and worsening.
- Improvement in physician assessed signs and symptoms and clinically relevant biomarkers (i.e. troponin T, N-terminal pro-brain B-type natriuretic peptide (NT-proBNP) and Cystatin-C).
- Consistent results on dyspnea and multiple other endpoints including WHF, length of stay and mortality in the supportive phase II Pre-RELAX-AHF trial in a similar patient population.
- Objective improvements on several important hemodynamic parameters (PCWP, PAP and SVR) demonstrated in the Central Hemodynamic study CRLX030A2201.

The benefits of serelaxin were also observed in the high risk subgroup of patients with moderate renal impairment (estimated glomerular filtration rate (eGFR) 30 to <60 mL/min/1.73 m2eGFR), in whom there is a significant unmet medical need for new AHF treatment options with favorable renal effects.

Ground 1b

Used methodology. The estimate of the effect size is not robust. The results were driven by the imputations that were applied for non-missing data after event of Worsening Heart Failure (WHF) with a large difference between the estimate according to the protocol and a conservative intention-to-treat approach based on observed values. Worsening Heart Failure cannot robustly be combined with the Visual Analogue Scale area under curve (VAS AUC) results and its use as an endpoint needs further justification."

Summary of the Applicant's response

Incorporating in-hospital WHF events or death into the primary efficacy analysis of patient-reported assessments of changes in dyspnea was prospectively defined in the study protocol of the RELAX-AHF Phase II/III program. Use of the worst-reported dyspnea score to supersede reported values after the WHF event is consistent with the fact that the in-hospital WHF event represents a patient's deteriorating clinical condition and failure of the randomized treatment which requires immediate initiation of rescue therapy. Reported dyspnea VAS scores after WHF are distorted by the use of rescue treatment and do not reflect the effect of the randomized

study treatment. Therefore, in order to appropriately represent the deteriorating clinical condition of patients with WHF in an ITT analysis, the study protocol specified the worst observed VAS score during the study to be used. A WHF event alters the in-hospital clinical course, as evidenced by prolongation of the hospital stay and increased risk of post-discharge mortality, which justifies the worst score assignment for the remainder of follow-up period in patients who experienced such an event. This was pre-specified in the study protocol and the statistical analysis plan and under the null hypothesis both groups had an equal chance to be affected by this. This strategy follows precedence in AHF clinical trials and other indications.

Importantly, several pre-specified and post-hoc sensitivity analyses were performed on the primary VAS AUC endpoint using various approaches to account for the occurrence of WHF. These included assignment of scores other than the pre-specified worst score (VAS = 0) to WHF events as well as alternative approaches that do not require the assignment of a value on the VAS scale. Taken together, these additional supportive analyses demonstrate that achievement of success on the VAS AUC primary endpoint in the RELAX-AHF trial did not depend on the assignment of a numerical score to patients with an unfavorable clinical course. If the clinical course of patients in the trial was characterized and ranked only according to clinical judgment, a favorable effect of serelaxin was consistently identified, and the strength of evidence for this effect was very similar to the protocol-specified analytical approach.

Several pre-specified and post-hoc sensitivity analyses were performed on the primary VAS AUC endpoint using various approaches to analyze occurrence of WHF, including assigning scores other than the pre-specified worst score (VAS = 0) to WHF events and alternative approaches that do not require the assignment of a value on the VAS scale. Overall, the results of sensitivity analyses were consistent with the pre-specified primary analysis.

Ground 1c

Background therapy. In the trial, the use of i.v. nitrates in the placebo arm was lower than expected based on current guidelines. Nitrates, similar to serelaxin, have vasodilating properties contributing to their therapeutic effect. Thus, this under-treatment with nitrates in the placebo arm may have well contributed to the observed difference in afterload compared with serelaxin during the period in which the primary end point was assessed, potentially affecting the size of the outcome measurement."

Summary of the Applicant's response

In the absence of scientific evidence, consensus in the medical community, treatment guidelines or agreed blood pressure (BP) targets, the use of vasodilators varies widely from one region, country or even institution to another and their use is based more on local experience and treatment algorithms. Most importantly, nitrate use in the RELAX-AHF trial is within the expected range of large international registries, especially if RELAX-AHF-like patients are considered.

Current treatment guidelines remain vague on when and how much nitrates should be used in the treatment of AHF, because there is a lack of evidence for clinically meaningful treatment benefit in this population. Hence, there is no consensus on the topic in the medical community, which is reflected in a wide variability of nitrate use in both the RELAX-AHF trial and AHF

registries. Most importantly, nitrate use in the RELAX-AHF trial is within the expected range of registries, especially if RELAX-AHF-like patients are considered.

The level of evidence supporting the use of nitrates in the treatment of AHF is weak. The current ESC AHF guidelines (McMurray et al 2012) list nitrates as a Class IIa/b Level B treatment recommendation, indicating that there is conflicting evidence and/or divergent opinion on their efficacy based on a single randomized trial:

"Although vasodilators such as nitroglycerin […] reduce preload and afterload and increase stroke volume, there is no robust evidence that they relieve dyspnea or improve other clinical outcomes."

The 2012 ESC AHF treatment guidelines do not indicate a BP target, nor do they recommend a predefined level of nitrate use. For hypertensive AHF the ESC hypertension guidelines are referenced instead (Mancia et al 2013), where a target SBP of <150 to <140 mmHg (depending on the age and comorbidity of the patient) is recommended. This highlights the absence of evidence to support a more aggressive use of anti-hypertensive medication, which is actually associated with worse outcome (Peacock et al 2011). In the RELAX-AHF study enrolment of patients on nitrates was restricted but not the use of nitrates during the study.

In the RELAX-AHF trial, the placebo group received more IV nitrates than the serelaxin group, which constitutes indirect proof for serelaxin's efficacy. In addition, data from the RELAX-AHF study does not provide evidence that the difference in SBP between the placebo and serelaxin group impacted the trial results.

Based on the overall totality of evidence available for serelaxin and unmet medical need in AHF, the Applicant consider that it is justified for serelaxin to be given consideration for a conditional marketing authorization at the current time.

Conditional Marketing Authorisation

The applicant proposed justifications for consideration of its application for a conditional Marketing Authorisation in accordance with Article 14(7) of the Regulation (EC) No 507/2006 based on the following claims:

- According to Commission Regulation No 507/2006 falling within the scope of Regulation 726/2004, medicinal products which aim to treat seriously debilitating or life-threatening diseases, such as Reasanz for the treatment of AHF, fall within the scope of conditional Marketing Authorization.

A justification for how serelaxin meets the additional requirements from Article 4 of Commission Regulation No 507/2006 is summarised below:

- **The benefit-risk balance:** the results of the RELAX-AHF and Pre-RELAX AHF studies indicate that serelaxin provides a robust improvement on a number of signs and symptoms of heart failure both patient-reported and physician assessed, and on the clinically relevant prevention of worsening heart failure (WHF). The patient-reported dyspnea results are supported by objective hemodynamic measures from the central hemodynamic study indicative of a reduction in congestion. In addition, significant effects

of serelaxin have been observed on long-term clinically important endpoints, in particular a reduction in Day 180 cardiovascular and all-cause mortality by 37%. These findings are accompanied by significant reductions in biomarkers associated with cardiac wall stress and cardiomyocyte injury and favorable effects on renal function. Improvement of the patient's clinical status is also evident through lower use of diuretics and faster transition to oral diuretics in the serelaxin-treated patients and a reduction of length of hospital stay of 0.9 days in the index heart failure hospitalization and of 0.3 days length of stay in the intensive care/coronary care unit. Serelaxin has a favorable safety profile. Hypotension has been identified as safety risk following serelaxin exposure that is explained by the serelaxin vasodilatory properties. This risk is manageable with selection of the appropriate patients (i.e., systolic blood pressure >125 mmHg prior to serelaxin treatment), careful blood pressure monitoring, and dose reduction or discontinuation during serelaxin infusion subsequent to the systolic blood pressure response. Overall, serelaxin has demonstrated a positive benefit-risk ratio with a benign safety profile and with clear and consistent benefits reproduced across two studies (Phase 3 RELAX-AHF study and Phase 2 Pre-RELAX-AHF) on signs and symptoms of congestion, reduction in worsening of heart failure, length of hospital stay, and mortality.

- **It is likely that the applicant will be able to provide comprehensive data:** The ongoing well-controlled Phase 3b study [RELAX AHF-2] (aiming to recruit 6375 patients with AHF) is designed to evaluate the efficacy of serelaxin compared to placebo when used on top of standard of care on cardiovascular mortality through 180 days. In addition, WHF, length of hospital stay, and all-cause mortality are assessed. This study is being conducted globally in overall 30 countries, including 22 EU countries. An interim analysis is planned by the time 60 % of the primary accrued events (308 cardiovascular deaths) are reached. Should the availability of serelaxin in the market impact the overall recruitment in the RELAX-AHF-2 study, Novartis will implement mitigation strategies, which include redistribution of the patient allocation to other non-impacted participating countries as well as potentially adding additional countries where the drug is not yet approved.
- **There is an unmet medical need in acute heart failure:** AHF remains a life-threatening disease and a major and growing public health problem with a very poor prognosis and high mortality following AHF episodes. In Europe, approximately 15 million patients suffer from heart failure, of which close to 50 percent are expected to die within 5 years after their first admission in the hospital. Its incidence increases and currently available AHF standard-of-care treatments do not address a number of treatments goals. Current AHF therapies are generally focused on achieving dyspnea relief and reducing congestion. None of the currently used therapies have been demonstrated to reduce in-hospital WHF events safely and no agents have demonstrated evidence of a long-term mortality reduction.
- **Benefits to public health:** any potential uncertainty about serelaxin's mortality reduction would be clarified, when the Phase 3b RELAX-AHF-2 study results are available. A conditional marketing authorisation in 2014 would allow patient access to serelaxin as a lifesaving treatment option earlier.

In addition to the grounds for re-examination the applicant presented at an oral explanation on 20 May 2014.

5.2 Scientific Advisory Group on Cardiovascular Issues (SAG CVS)

Following the receipt of the detailed grounds for the reexamination, the CHMP convened a Scientific Advisory Group on Cardiovascular Issues inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the applicant's response.

Report from the SAG CVS on 12th of May 2014

The SAG should comment on the grounds for negative opinion in view of the grounds for re-examination submitted.

Does the totality of data (haemodynamic, clinical and laboratory data) support a clinically relevant effect of serelaxin in the proposed target population or a sub-population thereof?

Has the Applicant demonstrated that serelaxin provides a clinically relevant improvement of dyspnoea?

It was acknowledged that formally speaking the RELAX–AHF study reached one of the co-primary endpoints: relieve of dyspnoea over the first 5 days of treatment compared to placebo as demonstrated by change in the mean area under curve (AUC) from baseline of the visual analogue scale (VAS), [2756 mm-hours on serelaxin versus 2308 mm-hours on placebo; p=0.0075]. Despite this and taking into account the totality of the data available to-date for serelaxin the SAG was of the opinion that no clinically relevant improvement of dyspnoea was demonstrated.
This is due to the fact that the results of the primary endpoint were driven by the imputations used in case of the event classified as worsening heart failure (WHF), where zero values were imputed for VAS, although these were not missing data. The experts noted that the trial was powered to detect a mean difference on 4 mm in the VAS scale; the treatment effect corresponded to 3.83 mm difference and only 1.5mm difference in sensitivity analyses using measured, instead of imputed values. Moreover the experts believed that 4mm difference on the 100-points scale is very small and clinically relevant improvement was believed to be at least 20 mm.

Possible relationship between the length of stay in the hospital and dyspnoea was noted (for serelaxin 0.9 days less than placebo) but it was pointed out that different factors could play a role in the duration of hospitalisation and clinical relevance of the finding is difficult to be interpreted (potential benefit should be coupled with reduction in re-admissions). Agents with a relatively short pharmacokinetic profile (half-life), without an oral analogue for maintenance therapy (e.g. serelaxin) may hasten stabilisation and discharge while administered in hospital. However, once withdrawn, they may potentially also incur a greater risk of acute heart failure (AHF) recrudescence and rehospitalisation. A drug used for heart failure with beneficial mortality effect would be expected to have an even greater impact on hospital re-admission and the fact that these two parameters move in opposite directions in this study increase the concern that the

observed mortality reduction may be a chance finding and as such should be regarded as hypothesis generating only.

Can the experts, focussing on the short term clinical course, comment the relevance of improvement in worsening of heart failure?

WHF as such was considered to be a valid endpoint in the opinion of experts. However they expressed a view that the trial was not appropriately designed to measure it; in particular the relationship between the use of diuretics and the WHF was not clearly understood. The definition of WHF used in the trial was found not sufficiently pre-specified and not stringent enough to interpret the relevance regarding its efficacy value. Therefore, WHF definition in such a context of hospital admission for AHF should be standardized, especially for the up-coming RELAX-AHF 2 trial.

It was also noted that the dose of diuretics used in the first 5 days since randomisation was relatively low (30 – 40 mg/day IV); much higher doses (up to 160mg IV BID) would be expected in some patients with AHF). The experts pointed out that probably the majority of patients included in the trial had pulmonary oedema rather than volume overload. Indeed a large proportion of patients were hypertensive with preserved left ventricular function.

Do you consider that serelaxin fulfils an unmet medical need, based on the current trial data on long-term outcome?

The experts confirmed that there is an unmet medical need regarding an appropriate treatment for AHF patients. However, it was clear, in the opinion of the Group, that serelaxin doesn't fulfil it based on the currently available data. Experts had doubts if this unmet medical need could be fulfilled when studying the AHF in the population of patients included specifically in the RELAX-AHF trial and given the objectives of this trial. Initial main objective of this study was to demonstrate efficacy on symptom reduction, which was not clearly obtained. Mortality was a safety endpoint, not an efficacy endpoint and results may have been obtained by chance.

So for justification of fulfilling such unmet medical need, data from the RELAX-AHF study are insufficient. In addition, in the past in AHF condition, several exploratory results on long term cardiovascular (CVS) mortality have not been confirmed with other drugs (nesiritide for example).

In the expert's opinion, is there a remaining concern that there was an insufficient treatment with nitrates in the control arm?

Taking into account the type of the AHF population studied in the RELAX-AHF, the use of nitrates should be around 60% according to the results of EuroHeart Failure Survey II (EHFS II; a survey on hospitalized AHF patients). Given the mean blood pressure (BP) was about 140 – 150 mm Hg, much higher use of nitrates (or other BP-reducing agents) would be expected. The nitrates would be mainstay of initial management of hypertension in this clinical context. Therefore, the experts believed, that the use of nitrates was below what is considered to be current clinical practice. The view of the Group was that clinical trial design may have led to less use of nitrates/BP lowering therapy in placebo arm by protocol (even if not explicit) exaggerating the apparent treatment effect. The inclusion criteria in the RELAX-AHF trial were also probably chosen in mind of reducing the incidence of seralaxin induced hypotension.

3. From your clinical perspective / experience and in view of the submitted data, do you have any plausible pathophysiological explanations for:

the discrepancy between predefined secondary efficacy outcomes ("Days alive out of hospital" and "CV death or re-hospitalization" at D60) and the observed mortality at day 180?

The experts did not consider the results at D60 ("Days alive out of hospital" and "CV death or re-hospitalization") and D180 (CVS mortality) necessarily contradictory. At D60 there seem to be a slight but not significant mortality advantage which becomes more apparent at D180. This could be a chance finding. Not sufficient data are available to draw conclusions (e.g. hospitalisation rate at D180 not known).

the difference in mortality between the treatment arms at day 180?

The experts could not find any plausible pathophysiological explanation for the difference in CVS mortality at D180. It was noted that the D180 mortality results were driven by stroke and sudden cardiac death (SCD) and that SCD is a well-recognised consequence of heart failure and may well complicate AHF. A difference in non-cardiovascular deaths was noted as well, increasing the likelihood that this is a chance observation (procedure related deaths 4:0, pulmonary deaths 2:0, sepsis 6:3, malignancy death 2:1, haematology death 1:0, together 15:4).
It was pointed out that patients in placebo arm were more often treated with inotropic agents (dopamine, dobutamine) from day 1 through day 5 which could have worsened the patient prognosis of the placebo group or which could indicate that they represented more serious cases of the AHF (although the percentages in each arm were small).
Given the observed and unexplained reduction in mortality, the SAG agrees that further study to more definitively answer this question is justified. It is hoped that this study will also more clearly define and adjudicate WHF in hospital, and examine rehospitalisation rate until D180.

The CHMP has considered the outcome of the advice provided by the SAG CVS.

5.3 Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and arguments presented in writing and in an oral explanation by the Applicant, considered the views of the Scientific Advisory Group and the justification for a conditional Marketing Authorisation.

Clinical relevance

It is concluded that the Applicant has failed to convincingly demonstrate a clinically relevant improvement in dyspnoea scores. The observed difference between the treatment groups of 4 mm on a 100 mm visual analogue scale must be regarded as small and even more so if the analysis with the observed values is considered with a difference of 1 mm. The difference expressed as 19% in overall dyspnoea score AUC is in itself difficult to translate into clinical relevance. Serelaxin was not associated with an increased proportion of 'patients with moderately or markedly improved dyspnea' on the Likert scale at the combined time points of 6, 12, and 24 hours compared to placebo (serelaxin: 26.9%, placebo: 25.9%; p=0.7024),

although numerical differences in favour of serelaxin were observed at each of the individual time points. The CHMP did not accept the Applicant's argumentation that the VAS-AUC-endpoint ought to be considered a multicomponent endpoint consisting of a) Change in dyspnoea score, b) Occurrence of in-hospital worsening heart failure and c) Death, and that it is "conceptually similar" to a composite endpoint. In the CHMP opinion the predefined primary endpoint is considered not more than a dyspnoea endpoint, which includes (an attempt for) correction for WHF and death. The Applicant's shift of focus on the clinical relevance of worsening of heart failure was not considered appropriate for addressing the CHMP's concern. Likert scores (better reflecting patients' perception of dyspnoea change) were not conclusively anchored to the related VAS observations to enable a statement on the clinical meaningfulness of the magnitude of effect.

Used methodology

It is concluded by the CHMP that the difference in VAS dyspnoea scores between the study groups is largely driven by WHF with the imputation method used. For the evaluation of the effects on dyspnoea the imputation rule must be regarded as anticonservative. A range of sensitivity analyses has been performed, many of which however still include a worst case imputation. Other analyses must be categorized as being post-hoc and defined in a data driven manner. Overall, the sensitivity analyses do not provide any essential new information in addition to the analysis based on observed values, which reflects an example of a worst case scenario. Though several (post-hoc) results would meet the predefined criterion for statistical significance, this is guided by the family-wise type I error control at 5%, i.e. the Applicants position does not consider the one-pivotal trial situation.

Altogether the analyses are not sufficiently convincing and a robust and large treatment effect is not demonstrated. It is concluded that the results of the predefined primary end-point alone fail to provide convincing results of such a nature as would be needed for a positive recommendation for approval in a one pivotal study application.

Background therapy

Overall, while it was apparent, that intravenous nitrates use in RELAX-AHF ranges in the lower regions of prescription frequency compared to other relevant datasets, it is also evident that reported nitrate use patterns vary considerably between regions and databases. A similar observation can be made between study sites within the Relax-AHF trial (i.e. prescription frequency ranging from 0 – 44%).

The CHMP noted the advice from the SAG CVS that taking into account the type of the AHF population studied in the RELAX-AHF, the use of nitrates would have been expected to be around 60% according to the results of EuroHeart Failure Survey II. Serelaxin and nitrates are assumed to largely exert comparable therapeutic effects (i.e. vasodilation and reduction of afterload) and a higher nitrate use might "compete" with serelaxin efficacy under this premise.

The CHMP noted that the slight imbalance between nitrate prescriptions did favour the placebo arm and that the additional analyses showed a trend towards better trial outcomes in those countries with a nitrate use rate >15% across the major endpoints; however this did not completely alleviate the concern.

In summary, the CHMP was of the view that the major objections identified in the original

assessment have not been resolved. There are still major concerns regarding the clinical relevance of the observed dyspnoea benefit, the methodology of data imputation as well as the issue of under-treatment with intravenous nitrates. The applicant´s decision to further investigate serelaxin's impact on cardiovascular mortality in the ongoing RELAX-AHF-II trial was considered by the CHMP the logical step towards confirming the promising, yet exploratory findings of RELAX-AHF. While it was agreed that the safety profile of serelaxin observed so far appears relatively benign, the robustness and clinical relevance of efficacy results was questioned by the CHMP. WHF and mortality findings, although promising, are considered exploratory in nature and confirmation from a second trial was considered necessary.

In conclusion, the CHMP believed that it is possible that the applicant would be able to provide comprehensive data following the completion of the RELAX-AHF-2 study and that there is unmet medical need in the treatment acute heart failure. The CHMP pointed out however that the benefits to public health of the immediate availability of serelaxin do not outweigh the risks inherent in the fact that additional data are still required. In the view of the CHMP, the current benefit-risk balance of serelaxin remains negative and conditional marketing authorisation can therefore not be granted.

5.4 Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the conditional Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

- The efficacy of Reasanz in the treatment of acute heart failure in adults with systolic blood pressure above 125 mm Hg on top of standard of care, including loop diuretics has not been sufficiently demonstrated;
- In the absence of established efficacy, a positive benefit-risk balance has not been established.

The CHMP considered that the requirements for a conditional approval laid down in Article 4 of the Commission Regulation (EC) No 507/2006, namely the benefit risk balance of the medicinal product, as defined in Article 1 (28a) of Directive 2001/83/EC, being positive, has not been fulfilled.

Furthermore, the CHMP, in light of the negative recommendation, has not concluded on the new active substance status at this time.

Divergent positions to the majority recommendation are appended to this report.

APPENDIX

DIVERGENT POSITION

Divergent Position

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the refusal of the granting of a Marketing Authorisation for Reasanz.

The reasons for divergent opinion were as follows:

We, the undersigned, are of the view that the totality of the provided data support a conclusion that serelaxin has clinically relevant beneficial effects in the intended target population and that its use can contribute to a favourable clinical course. We believe that the Applicant has addressed the CHMP grounds for refusal sufficiently well allowing a recommendation for a conditional approval.

London, 22 May 2014

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(Romania) (Denmark)

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(Malta) (Sweden)

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(Ireland) (Greece)

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