NOVARTIS

Clinical Development

RLX030/Serelaxin

Study No. CRLX030A2208/ NCT02151383

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

Statistical Analysis Plan (SAP)

Addendum 1

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Document type: SAP Documentation

Document status: Final

Release date: 09-Aug-2018

Number of pages: 5

Document History – Changes compared to previous final version of M3 (SAP) amendment 1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
09-Aug-2018	*Post DB lock*	*CSR addendum 1*	*Added additional analyses required for CSR addendum 1*	*NA*

Table of contents

Table of contents 3
List of abbreviations 4
1 Introduction 5
2 Statistical methods 5
2.1 Analysis of the Pharmacokinetics (PK) data 5
2.2 Analysis of the secondary efficacy endpoints 5

List of abbreviations

CSR	Clinical Study Report
CV	Coefficient of variation
CVP	Central venous pressure
LAP	Left atrial pressure
PAP	Pulmonary artery pressure
PK	Pharmacokinetics
RAP	Report and Analysis Process
SAP	Statistical Analysis Plan

1 Introduction

This document provides details of the additional statistical analyses required to support the completion of the abbreviated Clinical Study Report (CSR) addendum 1 for the study CRLX030A2208.

2 Statistical methods

The following analyses will follow the general information and definitions outlined in the study statistical analysis plan CRLX030A2208 M3 amendment 1 (previous final version of SAP), including the definitions of baseline, analysis sets, age cohorts and dose groups.

2.1 Analysis of the Pharmacokinetics (PK) data

The PK concentration will be summarized descriptively by age cohort within each dose group as well as in the overall group, and time point, using n, mean, standard deviation, coefficient of variation (CV), geometric mean, geometric CV, median, minimum, and maximum.

The PK analysis set will be used for the above analysis. This analysis will include the PK concentration data at all scheduled PK sampling time points, i.e., at 0, 2, 16, 22, 32, 40, 48 hr. during the infusion, at 0.5, 4, 8 hours post infusion or study drug discontinuation, and on day 14/day 28.

2.2 Analysis of the secondary efficacy endpoints

Summary statistics (n, mean, standard deviation, median, the first quartile (Q1), the third quartile (Q3), minimum, and maximum) will be provided by age cohort within each dose group as well as in the overall group for the measurement at each visit and change from baseline values for the following secondary efficacy variables:

- Central venous pressure (CVP)
- Left atrial pressure (LAP)
- Pulmonary artery pressure (PAP- systolic and diastolic)
- Central venous and arterial oxygen saturation
- Urine output
- Blood lactate levels (arterial and central venous lactate)

The safety set will be used for the above analyses. Data collected at the following assessment time points/visits will be included in the analyses: at baseline, prior to each dose escalation, at 48 hours post infusion start, and at 24 hours post end of infusion.

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Module 3 – Detailed Statistical Methodology

Amendment 1

Author(s): [redacted] Trial Statistician

Document type: RAP Documentation Amendment

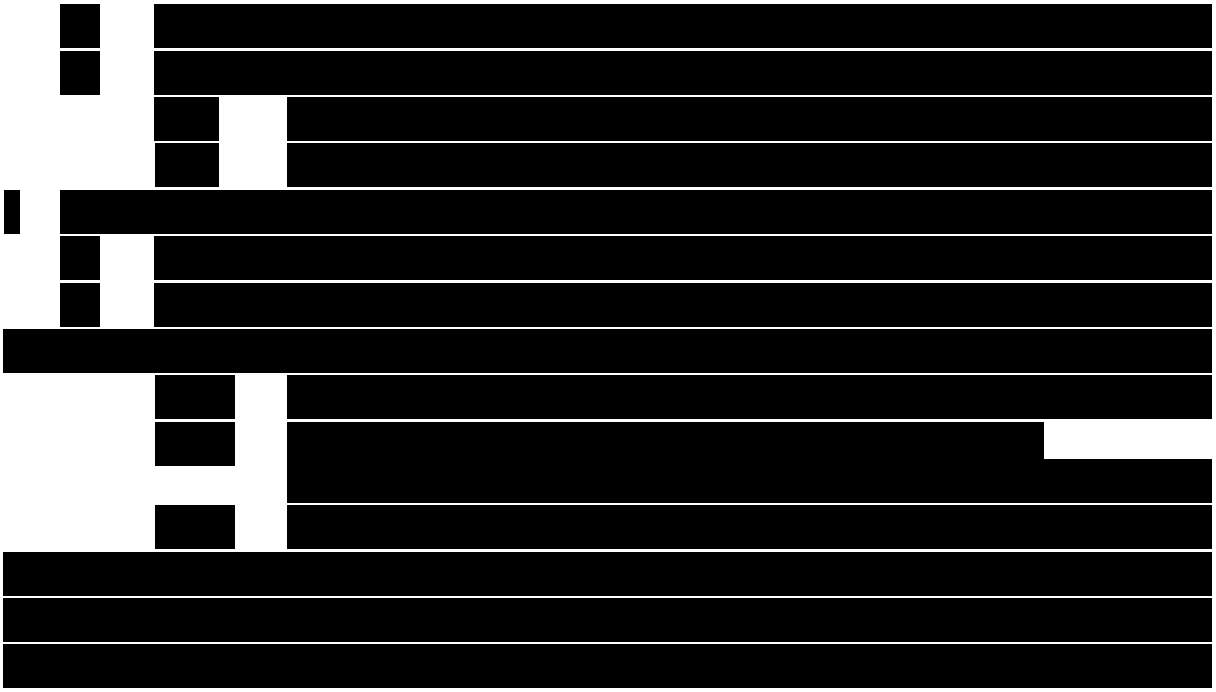
Document status: Final

Release date: 29-Jun-2017

Number of pages:

Table of contents

Table of contents 3
List of tables 4
List of abbreviations 5
[redacted]
1 Introduction 6
2 Analysis sets 7
3 Subgroup definitions 9
4 Baseline and post baseline definitions 9
5 Subject Disposition, background and demographic characteristics 10
5.1 Subject disposition 10
5.2 Protocol deviations 10
5.3 Background and demographic characteristics 10
5.4 Medical History 11
6 Study medication 11
7 Concomitant medication 11
8 Pharmacokinetic (PK) data 11
9 Selected vital signs for safety (SBP, DBP, HR and RR) 11
10 Adverse Events (AEs), SAEs and Deaths 11
11 Other data 12
12 Interim analyses 13
13 Sample size and power considerations 13
14 Appendix 1 - Reference 13
[redacted]



List of tables

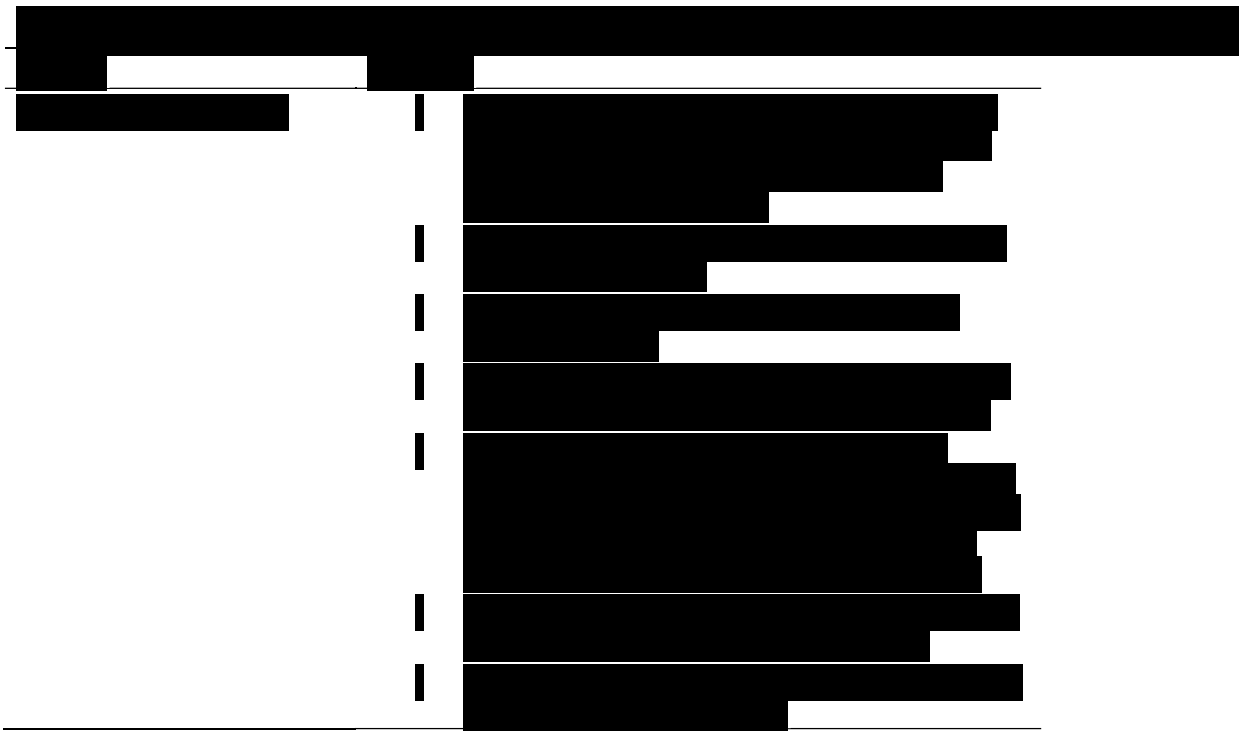
Table 2-1 Rules for subject classification in the analysis sets based on protocol deviations and non-protocol deviation classification criteria 8

Table 3-1 Specification of subgroups 9

List of abbreviations

AE	Adverse Event
BP	Blood Pressure
[redacted]	[redacted]
SBPDE	Systolic Blood Pressure Decrease Event
CSR	Clinical Study Report
[redacted]	[redacted]
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
ES	Enrolled Set
FAS	Full Analysis Set
HR	Heart Rate
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Affairs
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetics
PT	Preferred Term
PSRC	Pediatric Safety Review Committee
Q1	the First Quartile
Q3	the Third Quartile
RR	Respiratory Rate
SAE	Serious Adverse Event

SAF	Safety Set
SBP	Systolic Blood Pressure
SCR	Screened Set
SOC	System Organ Class
[redacted]	[redacted]
[redacted]	[redacted]



1 Introduction

This document provides details of the statistical analyses to support the completion of the abbreviated Clinical Study Report (CSR) for the study CRLX030A2208. Due to the early termination of the study, the planned analyses for a full/complete CSR (as outlined in the study protocol) may not provide clinically and/or statistically meaningful results. Therefore, an abbreviated CSR is planned for the study CRLX030A2208. No efficacy analysis will be performed for the abbreviated CSR: PK parameters and other derived efficacy parameters (as defined in the study protocol) will not be provided; Non-derived efficacy parameters (as outlined in the study protocol), if available, will be listed at the individual patient level. Other data will be listed with the following exceptions:

Summary tables will be provided for the following non-efficacy data:

- Disposition (see Section 5.1)
- Demographic and background characteristics (see Section 5.3)
- Safety data
    - Treatment emergent non-serious AEs (see Section 10)
    - Treatment emergent SAEs (see Section 10)
    - Treatment emergent AEs (including non-serious AEs and SAEs) (see Section 10)
    - Treatment emergent AEs leading to discontinuation (see Section 10)
    - Deaths (see Section 10)
    - Vital signs (selected) (see Section 9)
        - Systolic blood pressure (SBP)
        - Diastolic blood pressure (DBP)
        - Heart rate (HR)
        - Respiratory rate (RR)

In general, continuous variables will be summarized descriptively by n, mean, SD, median, minimum (min), Q1 (25th percentile), Q3 (75th percentile) and maximum (max), while categorical variables will be summarized by count and percentage of patients in each category. Unless otherwise specified, data will be summarized or listed by **dose group** (RLX low dose group: 3 µg/kg/day, 10 µg/kg/day and 30 µg/kg/day; RLX high dose group: 10 µg/kg/day, 30 µg/kg/day and 100 µg/kg/day) and **age cohort** (Age cohort 1: 6 to < 18 years; Age cohort 2: 1 to <6 years; Age cohort 3: infants 1 month to <1 year; Age cohort 4: neonates birth to <1 month).

Other data, including safety parameters, PK concentrations etc. will be listed at the individual patient level. In addition, graphical presentation of PK concentration vs. time will be provided.

[redacted]

2 Analysis sets

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

- **Screened set (SCR)** – All subjects for whom valid informed consent from a parent or legal guardian was obtained.
- **Enrolled set (ES)** – All subjects in the SCR to whom study treatment has been assigned, regardless of trial medication received.
- **Safety set (SAF)** – All subjects in the ES who were exposed to study drug regardless of the exposure and have at least one post-baseline safety assessment. Of note, the statement

that a subject had no adverse event (AE) also constitutes a safety assessment. Subjects will be analyzed according to treatment received.

- **The PK analysis set (PK)** will include all subjects with at least one available valid (i.e. not noted for exclusion) PK concentration measurement, who received study drug and experienced no protocol deviations with relevant impact on PK data. Subjects will be analyzed according to treatment received.

The number and percentage of patients in each analysis set will be summarized by age cohort within each treatment group if applicable and for all patients. Patients excluded from any analysis set will be listed for the safety population.

Table 2-1 Rules for subject classification in the analysis sets based on protocol deviations and non-protocol deviation classification criteria

Analysis set	Protocl Deviations (PDs) leading to the exclusion of a subject		Non-PD criteria leading to the exclusion of a subject
	Protocol Deviation ID	Description of the PD	
Screened set	INCL01	Written informed consent by parent/legal guardian was NOT obtained before any study-specific assessment, that is done specifically for the study, was performed.	
Enrolled set	INCL01	Written informed consent by parent/legal guardian was NOT obtained before any study-specific assessment, that is done specifically for the study, was performed.	
Safety set	INCL01	Written informed consent by parent/legal guardian was NOT obtained before any study-specific assessment, that is done specifically for the study, was performed.	No study medication given during the treatment period
PK analysis set	INCL01	Written informed consent by parent/legal guardian was NOT obtained before any study-specific assessment, that is done specifically for the study, was performed.	No study medication given during the treatment period; No valid PK concentration measurement

3 Subgroup definitions

In Table 3-1, we have listed all subgroups defined for this study. In general, subgroups will be defined based on baseline information. Age cohort will be used throughout the analyses. Count and percentage of etiology subgroups will be provided as part of the patient demographic and background information. [redacted]

Table 3-1 Specification of subgroups

Subgroup	Method of Derivation	Disposition /Background & demo. /Exposures	PK analysis	Safety
Age cohort (at screening [redacted]): Age cohort 1: 6 to <18 years; Age cohort 2: 1 to <6 years; Age cohort 3: 1 month* to <1 year; Age cohort 4: birth to <1 month*	eCRF	x	x	x
[redacted]				
Etiology subgroups [redacted]: Post-surgical etiology Medical etiology	eCRF	x		

*1 month = 30 days.

4 Baseline and post baseline definitions

Baseline definition

For the selected vital signs (SBP, DBP, HR and RR), baseline is defined as the measurement obtained on Day 1 [redacted], or the sample obtained at an earlier visit (scheduled or

unscheduled) which was closest to Day 1 [redacted], if the Day 1 [redacted] measurement is missing.

5 Subject Disposition, background and demographic characteristics

5.1 Subject disposition

The number and percentage of patients in each analysis set, safety patients who discontinued from the study and the reasons for discontinuation will be summarized by age cohort within each treatment group and in the overall group. The screened set (SCR) will be used.

In addition, the reasons for screen failures, based on inclusion/exclusion criteria, will be listed at the individual patient level for the SCR.

5.2 Protocol deviations

Protocol deviations will be pre-specified and finalized for analyses prior to database lock. All protocol deviations will be listed at the individual patient level for the SAF.

5.3 Background and demographic characteristics

The following demographic and background characteristics data [redacted] will be summarized descriptively (using n, mean, standard deviation, median, Q1, Q3, minimum, and maximum for continuous variables; or number and percentage for categorical variables) for the SAF by age cohort within each treatment, and in the overall group (Note: Categorical variables are underlined. Variables without an underline are continuous variables):

- Age (years)
- Sex: Male; Female
- Race: Caucasian; Black; Asian; Native American; Pacific Islander; Unknown; Other
- Ethnicity: Hispanic or Latino; East Asian; Southeast Asian; South Asian; West Asian; Russian; Mixed Ethnicity; Not Reported; Unknown; Other
- Weight (kg)
- Height (cm)
- Etiology: Post-surgical; Medical
- Genetic/chromosomal abnormalities: Yes; No; Unknown
- Clinical syndrome without genetic diagnosis: Yes; No; Unknown
- Malformation of an organ system other than the heart: Yes; No; Unknown

[redacted]

All demographic and background characteristic data, including delivery history (only for age cohort 3 or 4 patients) will be listed at the individual patient level for the SAF.

5.4 Medical History

Medical history entered on the medical history CRF page at screening [redacted] will be coded using the MedDRA dictionary. Medical history and protocol solicited events (only for post-surgical patients) will be listed at the individual patient level for the SAF.

6 Study medication

Data entered on the Dosage Administration Record CRF page will be listed at the individual patient level for the SAF. This will include dose prescribed (ug/kg/day), start/end date and time of the infusion, concentration (ug/ml), rate of infusion (mL/h) and reason for the dosage administered.

7 Concomitant medication

Prior and concomitant medications, continuous intravenous concomitant medications, surgical and medical procedures and use of mechanical ventilator will be listed at the individual patient level for the SAF. The medication name will be coded using therapeutic class (ATC code) and preferred term (PT).

8 Pharmacokinetic (PK) data

PK concentration data will be listed at the individual patient level for the SAF. Invalid PK concentration data will be noted. A graphical presentation will be employed to show individual serelaxin concentration-time (actual) profiles by age cohort within each dose group. These figures will be prepared for the PK analysis set.

9 Selected vital signs for safety (SBP, DBP, HR and RR)

Summary statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) will be provided by age cohort within each dose group for the measurement at each visit and change from baseline values for the following parameters for the safety population:

- Systolic blood pressure (SBP)
- Diastolic blood pressure (DBP)
- Heart rate (HR)
- Respiratory rate (RR)

10 Adverse Events (AEs), SAEs and Deaths

A treatment emergent adverse event is defined as an adverse event that occurs at or after the start of the study treatment. Treatment emergent adverse events including non-serious AEs, SAEs, AEs (including non-serious AEs and SAEs) and AEs leading to discontinuation will be

summarized descriptively (using number and percentage) by age cohort within each treatment group and in the overall group. Similarly, deaths will be summarized descriptively as appropriate. The number and percentage of these events will be presented by system organ class (SOC) and MedDRA preferred term (PT). All AEs will be listed at the individual patient level. These analyses will be performed for the SAF.

In addition, SAEs in screen failure patients will be listed at the individual patient level.

11 Other data

Other data will be listed at the individual patient level as appropriate. The following data will be listed for the SAF, and listings marked with "*" will be subject to data availability:

- Local lab (including chemistry, hematology and urinalysis)
- Central lab (including chemistry and hematology)
- Vital signs and clinical assessment
- Ventilation/respiratory parameters (if on mechanical ventilation)
- * Systolic Blood Pressure Decrease Event (SBPDE)
- * Vital signs – SBPDE monitoring
- * Ventilation/respiratory parameters – SBPDE monitoring
- * Vital signs – AE suggestive of Worsening Heart Failure (WHF) monitoring
- * Ventilation/respiratory parameters – AE suggestive of Worsening Heart Failure (WHF) monitoring
- Echocardiography
- [redacted]
- ECG
- [redacted]
- [redacted]

[redacted] eGFR (as part of the central laboratory data) will be calculated using the Schwartz formula (Schwartz et al. 2009): eGFR (mL/min/1.73m^2) = 0.41 x height (cm)/serum creatinine (mg/dL).

Mean arterial pressure, derived as [(2 x DBP) + SBP] ÷ 3 (Cywinski 1980), will be included in listings of the vital signs data. Notably abnormal vital signs (SBP, DBP, HR and RR) [redacted] will be noted in data listings.

12 Interim analyses

There will be no formal interim analysis for this study. However, there will be interim PK and safety data reviews by the Pediatric Safety Review Committee (PSRC). See Section 3.1 of the study protocol for study design details.

[redacted]

13 Sample size and power considerations

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

The sample size planned for the high-dose group (10/30/100 µg/kg/day) per age cohort will be 6 subjects or 3 subjects (see Section 3.1 of the study protocol v04 for the study design details). With a sample size of 6 subjects per age cohort, receiving RLX030 at various doses, there is ~80% probability to observe an adverse event with an underlying occurrence rate of 24% at least once for each cohort and dose combination during the study. With a sample size of 3 subjects per age cohort, receiving RLX030 at various doses, there is ~56% probability to observe an adverse event with an underlying occurrence rate of 24% at least once for each cohort and dose combination during the study.

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

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

These calculations were performed using nQuery.

14 Appendix 1 - Reference

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

Cywinski J (1980) The essentials in pressure monitoring *(*Martinus Nijhoff Publishers b.v. Boston): 23–24.