

Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

CLR325

CCLR325X2202

**A randomized, subject and investigator-blind,
placebo-controlled study of CLR325 in chronic stable heart
failure patients**

Statistical Analysis Plan (SAP)

Author(s):

Document type: SAP Documentation – NIBR

Document status: FINAL Amendment 1

Release date: 05-MAR-2019

Number of pages: 18

Property of Novartis
For business use only
May not be used, divulged, published or otherwise disclosed
without the consent of Novartis

Table of contents

Table of contents	3
List of tables	4
1 Introduction	5
1.1 Scope of document	5
1.2 Study reference documentation	5
1.3 Study objectives.....	5
1.3.1 Primary objective	5
1.3.2 Secondary objectives.....	5
1.4 Study design and treatment.....	6
2 First interpretable results (FIR)	7
4 Statistical methods: Analysis sets.....	8
5 Statistical methods for Pharmacokinetic (PK) parameters.....	9
5.1 Variables	9
5.2 Descriptive analyses	10
5.2.1 Handling of missing values/censoring/discontinuations.....	10
6 Statistical methods for Pharmacodynamic (PD) parameters	10
6.3 Statistical model, assumptions and hypotheses	13
6.3.1 Model checking procedures	14
7 Statistical methods for safety and tolerability data.....	14
7.1 Variables	14
7.2 Statistical model, assumptions and hypotheses	14
7.3 Descriptive analyses	15
7.3.1 Graphical presentation	16

8.1.5 Immunogenicity 17

List of tables

Table 4-1 Protocol deviation codes and analysis sets..... 9

1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial “**CCLR325X2202**”.

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

This SAP has been developed using Clinical Trial Protocol version v04 dated 31 October 2017.

1.3 Study objectives

1.3.1 Primary objective

- The primary objective of this study is to determine the safety and tolerability of an 18-hour i.v. infusion of CLR325 in stable heart failure patients.

1.3.2 Secondary objectives

The secondary objectives of this study are to:

- Determine the pharmacokinetics of CLR325, and the active metabolite, CQJ295, during an 18-hour i.v. infusion of CLR325 in heart failure patients.
- Determine the immunogenicity of an 18-hour i.v. infusion of CLR325 in heart failure patients.

1.4 Study design and treatment

This is a non-confirmatory, randomized, subject and investigator-blind, placebo-controlled study of an 18-hour infusion of CLR325 in stable heart failure patients (who may have a clinically indicated pulmonary artery catheter in place) to assess safety, tolerability, and pharmacokinetics in this patient population. Initially, one PA catheter cohort will be dosed: 6 patients with CLR325 and 2 with placebo randomized using a block randomization scheme. The first cohort of patients will be those with chronic stable heart failure. For subsequent cohorts, patients with acute decompensation who have been stabilized following hospital admission may also be enrolled. Following completion of the first cohort, subsequent cohorts may enroll concurrently as determined by the sponsor.

The study will be comprised of a screening period of up to 6 weeks (Day -45 to Day 1), a baseline period (Day 1), a treatment period (Day 1-2) and a follow up period (Days 3-28).

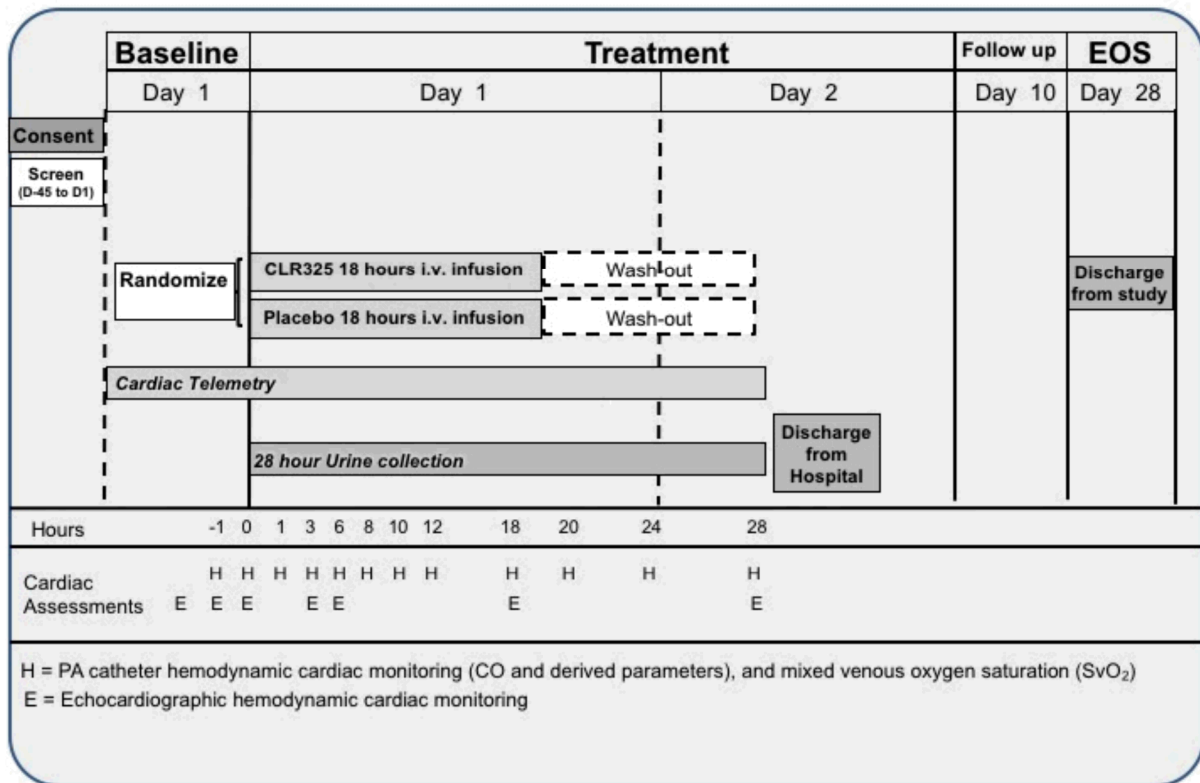
Each treatment period will be comprised of a baseline pre-dosing interval (hour -1 to hour 0), an inpatient dosing interval (hour 1 to hour 18), and an inpatient post-dosing interval (hour 18 to hour 28). In addition, patients will have a follow-up visit (Day 10) and an end-of-study visit on Day 28.

On Day -45 to -1, screening evaluations will be performed. Study inclusion/exclusion criteria as well as medication use will be assessed during the screening and baseline periods. Patients who meet all of the inclusion and none of the exclusion criteria at screening will report to the study site on Day 1 of the baseline period, at a time specified by the investigator, and if they continue to meet all inclusion and none of the exclusion criteria, will remain in-house until the final 28 hour inpatient assessment in the treatment period.

On Day 1, pre-dose laboratory evaluations, cardiac hemodynamic monitoring, and 3-lead continuous telemetry monitoring will be performed. The sponsor will pre-specify if hemodynamics are to be monitored by a PA catheter, echocardiography, or both for each cohort. For PA catheter cohorts, cardiac hemodynamics will be monitored continuously using a pulmonary artery catheter (that will have been placed for standard of care clinical indications by the subject's caregiver prior to randomization in the study) at select sites, a non-invasive bioreactance device. Intracardiac pressures (right atrial, pulmonary artery) will be recorded every hour during the treatment period. Thermodilution-based cardiac outputs will be obtained at hours -1, 0, 1, 3, 6, 8, 10, 12, 18, 20, 24, and 28 of the treatment period. If not needed for standard of care clinical indications, the pulmonary artery catheter may be removed after the final cardiac output measurement at hour 28. For echocardiographic cohorts, echocardiograms will be obtained during the treatment period as specified in the SOM. Note that the sponsor's decision regarding obtaining the echocardiogram will be applied uniformly across all patients in the cohort. All screening laboratory evaluation results must be available prior to dosing. Following the pre-dose procedures, eligible patients will be dosed intravenously. Post-dose evaluations will include routine laboratory evaluations, cardiac

monitoring, continuous telemetry monitoring, Patients may be released from the study site on Day 2, following completion of all 28-hour assessments, at the discretion of the investigator and if there are no safety concerns. The patients will be asked to return to the study site on Day 10 for a follow-up visit that will include a physical exam, routine laboratory evaluations, ECG evaluation, An end-of-study visit will be conducted on Day 28 and will include a physical exam, routine laboratory evaluations, ECG evaluation,

Figure 1-1 Study Design



2 First interpretable results (FIR)

First interpretable results (FIR) will be provided for this trial.

The template shows the analysis / results to be presented in the FIR. Study outputs required to be created at the time of the FIR will be highlighted in TFL shells document and marked as “Key” in the Programming Deliverables Tracker (PDT) output list.

4 Statistical methods: Analysis sets

For subjects for which the actual treatment received does not match the randomized treatment the treatment actually received will be used for all the analysis sets.

For safety and tolerability data, placebo subjects will be pooled across all cohorts, provided that there is no strong evidence against pooling.

The safety analysis set will include all subjects that received any study drug or placebo and no protocol deviations with relevant impact on Safety data.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and experienced no protocol deviations with relevant impact on PK data.

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from all (<i>safety</i>) analysis in case of these PDs:		Exclude subject completely from all (<i>safety</i>) analysis sets
Subjects are excluded from PK analysis in case of these PDs:		Exclude subject from PK analysis set
S02	Major study treatment deviation	Yes
Subjects are excluded from PD analysis in case of these PDs:		
S02	Major study treatment deviation	Yes
Subjects are excluded from PK analysis in case of these PDs:		Exclude subject from PK analysis sets
S02	Major study treatment deviation	Yes

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

5 Statistical methods for Pharmacokinetic (PK) parameters

5.1 Variables

The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher): C_{max}, T_{max}, AUC_{0-18h}, AUC_{last}, AUC_{0-28h}, AUC_{inf}, T_{1/2}, CL (CLR325 only), V_{ss} (CLR325 only), CL_r, and Ae₀₋₂₈ from the plasma concentration-time or urine concentration and collection volume data. The renal clearance (CL_r) will be determined based on AUC and Ae available for the same time period.

The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of T1/2 will include at least 3 data points after Cmax. If the adjusted R2 value of the regression analysis of the terminal phase will be less than 0.75, no values will be reported for T1/2, AUCinf, Vss (CLR325 only), and CL (CLR325 only).

5.2 Descriptive analyses

CLR325 plasma concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Pharmacokinetic parameters will be listed by treatment and subject. Descriptive summary statistics will be provided by treatment and time point.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values.

5.2.1 Handling of missing values/censoring/discontinuations

All drug concentrations below the lower limit of quantification (LLOQ) will be reported as “zero” and will be treated as zero for calculation of PK parameters.

6.3 Statistical model, assumptions and hypotheses

6.3.1 Model checking procedures

In case of convergence issues, the covariance matrix that best fit the data will be chosen. Diagnostic plots will be provided.

7 Statistical methods for safety and tolerability data

The primary objective for this study will characterize the safety of 18-hour i.v. infusion of CLR325 in patients with chronic heart failure.

7.1 Variables

The primary variable will be the occurrence of adverse events in patients in the study.

Other safety variables are vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, as well as subject demographics, baseline characteristics, and treatment information.

7.2 Statistical model, assumptions and hypotheses

All information obtained on adverse events will be displayed by treatment and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

The occurrence of adverse events will be examined by treatment. Both the total number of adverse events, and the preferred term for the adverse event will be compared by treatment.

7.3 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment and subject. Summary statistics will be provided by treatment.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment and subject.

Treatment

Data for total dose of infusion, infusion rate and total time of infusion will be listed by treatment and subject.

Data for concomitant therapies will be listed by treatment and subject.

Vital signs

All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged.

Summary statistics will be provided by treatment and visit/time.

Automatic implantable cardioverter defibrillator (AICD) interrogation

If patients have an AICD in place, the information gathered from the interrogation (e.g., number of runs of ventricular tachycardia) will be recorded listed by treatment and subject.

Safety events reported in AICD include episodes of anti-tachycardia pacing, AICD shocks delivered, runs of ventricular tachycardia, runs of supra-ventricular tachycardia and atrial fibrillation. These events will be summarized in the same fashion as adverse events, that is, the number and percentage of subjects with these events will be tabulated with a breakdown by treatment. A subject with multiple (≥ 1) occurrences of an event (or $\geq 1\%$ time in atrial fibrillation for the event of atrial fibrillation particularly) is only counted once towards the total of this body system.

Cardiac Holter and telemetry monitoring

Cardiac Holter monitoring data, as well as real time cardiac telemetry data, will be listed by treatment and subject.

Safety assessments related to ventricular arrhythmia from the Holter monitoring include the numbers of runs, couplets and isolated events of premature ventricular contractions. For three time windows: pre-infusion, infusion and post-infusion, the numbers per hour of these events will be calculated and further summarized by window and treatment group.

Fluid input and output

Fluid intake and output during the treatment period will be listed by treatment and subject. Summary statistics will be provided by treatment and visit/time.

7.3.1 Graphical presentation

Mean (SE) plots of vital signs, ECG evaluations, and lab evaluations will be produced by time from baseline to the end of treatment (hour 28).

8.1.5 Immunogenicity

All immunogenicity results will be listed by subject and visit/time.

Anti-CLR325 and anti-apelin antibodies in serum will be analyzed pre-dose, day 10 and day 28. Summary statistics will be provided for anti-CLR325 and anti-apelin antibodies. Immunogenicity will also be reported using the binary assessment “Yes” or “No”. For immunogenicity positive samples (“Yes”), the corresponding titer will be reported.

If for any reason the IG data delivery is delayed, a CSR addendum may be considered for the reporting.

