NOVARTIS

Clinical Development

LCZ696

CLCZ696B2319 / NCT02678312

Multicenter, open-label, study to evaluate safety, tolerability, pharmacokinetics and, pharmacodynamics of LCZ696 followed by a 52-week randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared with enalapril in pediatric patients from 1 month to < 18 years of age with heart failure due to systemic left ventricle systolic dysfunction

Statistical Analysis Plan (SAP) for China Sub-CSR

Author: Statistician, [redacted];

Document type: SAP Documentation

Document status: Final version

Release date: 25-October-2021

Number of pages: 21

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
25-Oct-2021	Prior to DB lock	Creation of final version	N/A - First version	NA

Table of contents

List of abbreviations

ACE	Angiotensin-Converting Enzyme
AE	Adverse Event
AMI	Acute Myocardial Infarction
ARB	Angiotensin Receptor Blockers
ATC	Anatomical Therapeutic Classification
CEC	Clinical Event Committee
CRF	Case Report Form
CV	Cardiovascular
CSR	Clinical Study report
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
HF	Heart failure
PCI	Percutaneous Coronary Intervention
PRO	Patient-reported Outcomes
RAAS	Renin-Angiotensin-Aldosterone System
SAP	Statistical Analysis Plan
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

Data will be analyzed according to the planned statistical analyses outlined in the CLCZ696B2319 study protocol (version 06) Section 9 and the CLCZ696B2319 SAP document.

This document is created to identify the required tables and figures for the submission in China.

1.1 Study design

This study uses a seamless design which consists of two parts.

Part 1 is a multi-center, open-label, study to evaluate safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of LCZ696 in pediatric patients (1 month to <18 years) with heart failure due to systemic left ventricle systolic dysfunction (left ventricular ejection fraction [LVEF] ≤ 40% or fractional shortening ≤ 20%). Eligible patients will be placed into three age groups (Age Group 1: 6 years to < 18 years, Age Group 2: 1 year to < 6 years, and Age Group 3: 1 month to < 1 year). Patient enrollment will start sequentially from the eldest age group to the youngest age group.

For each age group, available PK/PD and safety data will be reviewed to confirm or modify the doses. After completion of the PK/PD assessment visit, patients can either be maintained on open-label enalapril or their standard of care HF medical regimen until Part 2. Patients in each age group can enroll in Part 2 after the target dose for that age group is determined based on Part 1 data for the corresponding age cohort. Patients that discontinue from Part 1 (PK/PD) will be allowed to screen and enroll for participation in Part 2.

Part 2: This is a randomized, double-blind, parallel-group, active controlled, 52-week study to evaluate the efficacy, safety, and tolerability of LCZ696 compared to enalapril in pediatric HF patients (1 month to < 18 years). A screening epoch of up to 3 weeks will be used to assess eligibility. Three hundred and sixty eligible patients will be randomized to one of the two treatment arms (LCZ696 vs. enalapril) and continue treatment for 52 weeks duration. Both hospitalized patients and outpatients are eligible. Chronic HF patients that are either previously treated for HF or newly diagnosed are eligible.

An interim efficacy analysis is planned to be performed when at least 180 patients (at least 36 patients from each age group) have completed the study (i.e., reached a positively adjudicated event in Category 1 or completed the 1 year study visit), and at least 40 patients have had an event in Category 1 or 2. Further details about interim analysis are provided in Section 2.15 in the CLCZ696B2319 SAP document.

If not stopped early for efficacy or futility based on the interim analysis, Part 2 will continue until at least 360 patients have completed the study and at least 80 patients have an event in Category 1 or 2. If necessary, study enrollment will continue beyond 360 patients in order to obtain at least 80 patients with an event in Category 1 or 2, based on event prediction.

A penalty-free blinded sample size adjustment may be made in the latter part of the study to ensure a power of 80% for the study.

For the submission in China, only outcomes assessed in Part 2 will be analysed because there is no patients from mainland China included in Part 1.

1.2 Study objectives and endpoints – Part 2

1.2.1 Primary objective

The primary objective of Part 2 is to determine whether LCZ696 is superior to enalapril for the treatment of HF as assessed using a global rank endpoint in pediatric HF patients.

1.2.2 Secondary objectives

- To determine whether LCZ696 is superior to enalapril in delaying time to first occurrence of the composite of either Category 1 or 2 events (e.g. death, worsening HF)
- To determine whether LCZ696 is superior to enalapril for improving NYHA/ROSS functional class
- To determine whether LCZ696 is superior to enalapril for improving the PGIS score
- To assess the safety and tolerability of LCZ696 compared to enalapril in pediatric patients with HF
- To characterize the population PK of LCZ696 exposure in pediatric patients with HF.

[redacted]

2 Statistical methods

2.1 Data analysis general information

The final CSR analysis will be performed by Novartis. The same analysis method used in the global SAP will be used for the each of the specified endpoints in this SAP. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

Since the study was designed for the global population and all below indicated subpopulations are subsets of the Asia/Pacific subset of the global population and are not pre-specified for the design, the analysis results from them must be cautiously interpreted and no results can be confirmatory.

The PK results in Chinese may be summarized and analyzed in a separate report.

2.1.1 General definitions

The general definitions are the same as the main SAP for CLCZ696B2319.

2.2 Analysis sets

The analysis sets are the same as the main SAP for CLCZ696B2319. Each sub-population is defined as below:

China mainland Population

The China Mainland Population (CHN) refers to patients from Mainland China.

Chinese Population

The Chinese Population (CHINESE) refers to all Chinese patients regardless of residential country (this includes Chinese patients from Mainland China, Taiwan, Singapore and USA).

East Asia Population

The East Asia Population (EASTASIA) refers to patients from East Asia, including: China mainland, Taiwan , Japan , Korea, Singapore and Thailand.

3 List of tables/figure

Below is the list of tables and figures specified for each of the regional subpopulation. The China Mainland population (CHN) will be used as an example and the same list of tables and figures will be generated for each of the regional subpopulation, i.e. Chinese population (CHINESE), East Asia population (EASTASIA).

Table 10-1_CHN Part 2 patient disposition - double-blind epoch (Randomized Set: China Mainland Population)
Programming note: Refer to Table 10-1 in CLCZ696B2319 RAP Section 14

Table 10-2_CHN Part 2 study treatment disposition - double-blind epoch (Randomized Set: China Mainland Population)
Programming note: Refer to Table 10-2 in CLCZ696B2319 RAP Section 14

Table 11-1_CHN Part 2 demographic and baseline characteristics (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 11-1 in CLCZ696B2319 RAP Section 14

Table 11-2_CHN Part 2 pediatric heart failure history (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 11-2 in CLCZ696B2319 RAP Section 14

Table 11-3_CHN Part 2 global rank endpoint - patient allocation (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 11-3 in CLCZ696B2319 RAP Section 14

Table 11-4_CHN Part 2 time to first positively adjudicated Category 1 or Category 2 event during the double-blind epoch - Kaplan-Meier estimates - cumulative event rate (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 11-4 in CLCZ696B2319 RAP Section 14

Table 12-1_CHN Part 2 treatment emergent (newly occurring or worsening) adverse events of special interest (TEAESIs) during the double-blind epoch, regardless of study treatment relationship - exposure adjusted incidence rate (EAIR) (Part 2 Safety Set)
Programming note: Refer to Table 12-1 in CLCZ696B2319 RAP Section 14

Table 14.1-1.1.3_CHN Part 2 patient disposition - double-blind epoch (Randomized Set: China Mainland Population)
Programming note: Refer to Table 14.1-1.1.3 in CLCZ696B2319 RAP Section 14

Table 14.1-1.1.4_CHN Part 2 patient disposition - double-blind epoch by COVID-19 period (Randomized Set: China Mainland Population)
Programming note: Refer to Table 14.1-1.1.4 in CLCZ696B2319 RAP Section 14

Table 14.1-1.3_CHN Part 2 study treatment disposition - double-blind epoch (Randomized Set: China Mainland Population)
Programming note: Refer to Table 14.1-1.3 in CLCZ696B2319 RAP Section 14

Table 14.1-1.3.1_CHN Part 2 study treatment disposition - double-blind epoch COVID-19 period (Randomized Set: China Mainland Population)
Programming note: Refer to Table 14.1-1.3.1 in CLCZ696B2319 RAP Section 14

Table 14.1-1.4.2_CHN Part 2 analysis sets (Randomized set: China Mainland Population)
Programming note: Refer to Table 14.1-1.4.2 in CLCZ696B2319 RAP Section 14

Table 14.1-1.5.2_CHN Part 2 criteria leading to exclusion from analysis sets (Randomized Set: China Mainland Population)
Programming note: Refer to Table 14.1-1.5.2 in CLCZ696B2319 RAP Section 14

Table 14.1-1.6.2_CHN Protocol deviations of Part 2 patients (Randomized Set: China Mainland Population)
Programming note: Refer to Table 14.1-1.6.2 in CLCZ696B2319 RAP Section 14

Table 14.1-1.6.3_CHN Protocol deviations of Part 2 patients by COVID-19 period (Randomized Set: China Mainland Population)
Programming note: Refer to Table 14.1-1.6.3 in CLCZ696B2319 RAP Section 14

Table 14.1-1.6.4_CHN COVID-19 related protocol deviations for part2 patients (Randomized Set: China Mainland Population)
Programming note: Refer to Table 14.1-1.6.4 in CLCZ696B2319 RAP Section 14

Table 14.1-3.1.2_CHN Part 2 demographic and baseline characteristics (Full Analysis Set: China Mainland Population)

Programming note: Refer to Table 14.1-3.1.2 in CLCZ696B2319 RAP Section 14

Table 14.1-3.2.2_CHN Part 2 medical history - by primary system organ class and preferred term (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 14.1-3.2.2 in CLCZ696B2319 RAP Section 14

Table 14.1-3.3.2_CHN Part 2 pediatric heart failure history (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 14.1-3.3.2 in CLCZ696B2319 RAP Section 14

Table 14.1-3.4.2_CHN Part 2 medical history possibly contributing to liver dysfunction (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 14.1-3.4.2 in CLCZ696B2319 RAP Section 14

Table 14.2-2.1_CHN Part 2 global rank endpoint - patient allocation (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 14.2-2.1 in CLCZ696B2319 RAP Section 14

Table 14.2-2.3_CHN Part 2 Clinical events for Category 1 and 2 summary (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 14.2-2.3 in CLCZ696B2319 RAP Section 14

Table 14.2-2.2.1_CHN Part 2 global rank endpoint - primary rank score (PACE) - Mann-Whitney analysis - LOCF (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 14.2-2.2.1 in CLCZ696B2319 RAP Section 14

Table 14.2-2.4.1_CHN Part 2 global rank endpoint - response category (PACE) - Mann-Whitney analysis - LOCF (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 14.2-2.4.1 in CLCZ696B2319 RAP Section 14

Table 14.2-3.1.1_CHN Part 2 time to first positively adjudicated Category 1 or Category 2 event during the double-blind epoch - Kaplan-Meier estimates - cumulative event rate (Full Analysis Set: China Mainland Population)

Programming note: Refer to Table 14.2-3.1.1 in CLCZ696B2319 RAP Section 14

Table 14.2-3.1.2_CHN Part 2 time to first positively adjudicated Category 1 or Category 2 event during the double-blind epoch - Cox proportional hazard model (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 14.2-3.1.2 in CLCZ696B2319 RAP Section 14

Table 14.2-3.2.1_CHN Part 2 time to first investigator reported Category 1 or Category 2 event during the double-blind epoch - Kaplan-Meier estimates - cumulative event rate (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 14.2-3.2.1 in CLCZ696B2319 RAP Section 14

Table 14.2-3.2.2_CHN Part 2 time to first investigator reported Category 1 or Category 2 event during the double-blind epoch - Cox proportional hazard model (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 14.2-3.2.2 in CLCZ696B2319 RAP Section 14

Figure 14.2-3.1.1_CHN Part 2 time to first positively adjudicated Category 1 or Category 2 event during the double-blind epoch - Kaplan-Meier estimates - cumulative event rate (Full Analysis Set: China Mainland Population)
Programming note: Refer to Figure 14.2-3.1.1 in CLCZ696B2319 RAP Section 14

Figure 14.2-3.2.1_CHN Part 2 time to first investigator reported Category 1 or Category 2 event during the double-blind epoch - Kaplan-Meier estimates - cumulative event rate (Full Analysis Set: China Mainland Population)
Programming note: Refer to Figure 14.2-3.2.1 in CLCZ696B2319 RAP Section 14

Table 14.2-4.1_CHN Part 2 NYHA/ROSS classification - proportional cumulative odds model – post Category 1 event set to worsened (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 14.2-4.1 in CLCZ696B2319 RAP Section 14

Table 14.2-4.3_CHN Part 2 NYHA/ROSS classification - shift from baseline - by visit and treatment group (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 14.2-4.3 in CLCZ696B2319 RAP Section 14

Table 14.2-4.5_CHN Part 2 NYHA/ROSS classification - proportional cumulative odds model – post Category 1 event set to worsened (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 14.2-4.5 in CLCZ696B2319 RAP Section 14

Table 14.2-5.1_CHN Part 2 patient global impression of severity (PGIS) - proportional cumulative odds model – post Category 1 event set to worsened (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 14.2-5.1 in CLCZ696B2319 RAP Section 14

Table 14.2-5.3_CHN Part 2 patient global impression of severity (PGIS) - shift from baseline - by visit (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 14.2-5.3 in CLCZ696B2319 RAP Section 14

Table 14.2-5.5_CHN Part 2 patient global impression of severity (PGIS) - proportional cumulative odds model - post Category 1 event set to worsened - without cutoff (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 14.2-5.5 in CLCZ696B2319 RAP Section 14

Table 14.2-8.2_CHN Part 2 biomarkers – summary (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 14.2-8.2 in CLCZ696B2319 RAP Section 14

Table 14.2-8.3_CHN Part 2 NT-proBNP – change from baseline – Mixed Model for Repeated Measures (MMRM) (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 14.2-8.3 in CLCZ696B2319 RAP Section 14

Figure 14.2-8.3_CHN Part 2 biomarkers - geometric mean line plot (Full Analysis Set: China Mainland Population)
Programming note: Refer to Figure 14.2-8.3 in CLCZ696B2319 RAP Section 14

Table 14.2-9.1_CHN Part 2 total (first and recurrent) positively adjudicated Category 1 and Category 2 events - LWYY analysis (Full analysis set: China Mainland Population)
Programming note: Refer to Table 14.2-9.1 in CLCZ696B2319 RAP Section 14

Table 14.2-9.2_CHN Part 2 total (first and recurrent) investigator reported Category 1 and 2 events - LWYY analysis (Full analysis set: China Mainland Population)
Programming note: Refer to Table 14.2-9.2 in CLCZ696B2319 RAP Section 14

Table 14.2-9.3_CHN Part 2 Number (%) of total (first and recurrent) positively adjudicated Category 1 and Category 2 events - (Full Analysis Set: China Mainland Population)
Programming note: Refer to Table 14.2-9.3 in CLCZ696B2319 RAP Section 14

Table 14.3-1.2_CHN Part 2 study treatment - treatment exposure during the double-blind epoch (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-1.2 in CLCZ696B2319 RAP Section 14

Table 14.3-1.3_CHN Part 2 study treatment – Weight based daily dose and dose level - by visit (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-1.3 in CLCZ696B2319 RAP Section 14

Table 14.3-1.4_CHN Part 2 study treatment - mean weight based daily dose and mean dose level during the double-blind epoch (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-1.4 in CLCZ696B2319 RAP Section 14

Table 14.3-1.5_CHN Part 2 study treatment - dispensing level and dose level - by visit (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-1.5 in CLCZ696B2319 RAP Section 14

Table 14.3-1.6_CHN Part 2 study treatment - last recorded dose during the double-blind epoch (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-1.6 in CLCZ696B2319 RAP Section 14

Table 14.3-1.7_CHN Part 2 study treatment - dose down titration and dose interruption during the double-blind epoch (Part 2 Safety Set: China Mainland Population)

Programming note: Refer to Table 14.3-1.7 in CLCZ696B2319 RAP Section 14

Table 14.3-1.8_CHN Part 2 study treatment - time to first dose of each dose level during the double-blind epoch - Kaplan-Meier estimates - cumulative event rate (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-1.8 in CLCZ696B2319 RAP Section 14

Table 14.3-1.9_CHN Part 2 study treatment - time to permanent discontinuation of the study drug (excluding discontinuation due to death) during the double-blind epoch - Kaplan-Meier estimates - cumulative event rate (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-1.9 in CLCZ696B2319 RAP Section 14

Figure 14.3-1.1_CHN Part 2 study treatment - time to first dose of each dose level during the double-blind epoch - Kaplan-Meier estimates - cumulative event rate (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Figure 14.3-1.1 in CLCZ696B2319 RAP Section 14

Figure 14.3-1.2_CHN Part 2 study treatment - time to permanent discontinuation of the study drug (excluding discontinuation due to death) during the double-blind epoch - Kaplan-Meier estimates - cumulative event rate (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Figure 14.3-1.2 in CLCZ696B2319 RAP Section 14

Table 14.3-1.2.3_CHN Part 2 prior medications - by anatomical therapeutic classification (ATC) and preferred term (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-1.2.3 in CLCZ696B2319 RAP Section 14

Table 14.3-1.2.4_CHN Part 2 concomitant medications by anatomical therapeutic classification (ATC) and preferred term (Part 2 Safety Set)
Programming note: Refer to Table 14.3-1.2.4 in CLCZ696B2319 RAP Section 14

Table 14.3-1.3.3_CHN Part 2 prior heart failure and cardiovascular medications - by anatomical therapeutic classification (ATC) and preferred term (Part 2 Safety Set: China Mainland Population)

Programming note: Refer to Table 14.3-1.3.3 in CLCZ696B2319 RAP Section 14

Table 14.3-1.3.4_CHN Part 2 concomitant heart failure and cardiovascular medications - by anatomical therapeutic classification (ATC) and preferred term (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-1.3.4 in CLCZ696B2319 RAP Section 14

Table 14.3-1.4.3_CHN Part 2 prior non-drug therapies - by primary system organ class, preferred term (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-1.4.3 in CLCZ696B2319 RAP Section 14

Table 14.3-1.4.4_CHN Part 2 concomitant non-drug therapies - by primary system organ class, preferred term (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-1.4.4 in CLCZ696B2319 RAP Section 14

Table 14.3-2.1.2_CHN Part 2 laboratory parameters - test values and change from baselines - by visit - hematology (local laboratory) (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-2.1.2 in CLCZ696B2319 RAP Section 14

Table 14.3-2.1.3_CHN Part 2 laboratory parameters - test values and change from baselines - by visit - hematology (central laboratory) (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-2.1.3 in CLCZ696B2319 RAP Section 14

Table 14.3-2.2.2_CHN Part 2 laboratory parameters - test values and change from baselines - by visit - biochemistry (local laboratory) (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-2.2.2 in CLCZ696B2319 RAP Section 14

Table 14.3-2.2.3_CHN Part 2 laboratory parameters - test values and change from baselines - by visit - biochemistry (central laboratory) (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-2.2.3 in CLCZ696B2319 RAP Section 14

Table 14.3-2.7.2_CHN Part 2 laboratory parameters - clinically notable events during the double-blind epoch - hematology (local laboratory and central laboratory) (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-2.7.2 in CLCZ696B2319 RAP Section 14

Table 14.3-2.8.2_CHN Part 2 laboratory parameters - clinically notable events during the double-blind epoch - biochemistry (local laboratory and central laboratory) (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-2.8.2 in CLCZ696B2319 RAP Section 14

Table 14.3-2.9.2_CHN Part 2 post-baseline abnormal liver enzymes during the double-blind epoch (local laboratory and central laboratory) (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-2.9.2 in CLCZ696B2319 RAP Section 14

Table 14.3-2.10.2_CHN Part 2 newly occurring abnormal liver enzymes during the double-blind epoch (local laboratory and central laboratory) (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-2.10.2 in CLCZ696B2319 RAP Section 14

Table 14.3-2.11.2_CHN Part 2 renal event during the double-blind epoch (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-2.11.2 in CLCZ696B2319 RAP Section 14

Table 14.3-3.1.2_CHN Part 2 vital signs - test values and change from baselines - by visit (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-3.1.2 in CLCZ696B2319 RAP Section 14

Table 14.3-3.2.2_CHN Part 2 vital signs - clinically notable events during the double-blind epoch (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-3.2.2 in CLCZ696B2319 RAP Section 14

Table 14.3-3.3.2_CHN Part 2 vital signs - newly occurring clinically notable events during the double-blind epoch (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-3.3.2 in CLCZ696B2319 RAP Section 14

Figure 14.3-3.1.3_CHN Part 2 vital signs – heart rate - mean line plot (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Figure 14.3-3.1.3 in CLCZ696B2319 RAP Section 14

Figure 14.3-3.2.3_CHN Part 2 vital signs – - systolic blood pressure - mean line plot (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Figure 14.3-3.2.3 in CLCZ696B2319 RAP Section 14

Figure 14.3-3.3.3_CHN Part 2 vital signs - diastolic blood pressure - mean line plot (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Figure 14.3-3.3.3 in CLCZ696B2319 RAP Section 14

Table 14.3-4.1.2_CHN Part 2 electrocardiogram (ECG) - test values and change from baselines - by parameter and visit (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-4.1.2 in CLCZ696B2319 RAP Section 14

Table 14.3-4.2.2_CHN Part 2 electrocardiogram (ECG) - new onset clinically significant abnormality (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3-4.1.2 in CLCZ696B2319 RAP Section 14

Section 14.3.1_CHN Displays of adverse eventsTable (China Mainland Population)
Programming note: Refer to Section 14.3.1 in CLCZ696B2319 RAP Section 14

Table 14.3.1-1.2_CHN Part 2 treatment emergent adverse events - overall summary (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3.1-1.1.2 in CLCZ696B2319 RAP Section 14

Table 14.3.1-2.2_CHN Part 2 treatment emergent adverse events (TEAEs) during the double-blind epoch (regardless of study treatment relationship) - by primary system organ class, preferred term (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3.1-2.2 in CLCZ696B2319 RAP Section 14

Table 14.3.1-3.2_CHN Part 2 treatment emergent adverse events (TEAEs) during the double-blind epoch (regardless of study treatment relationship) - by primary system organ class, preferred term, maximum severity (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3.1-3.2 in CLCZ696B2319 RAP Section 14

Table 14.3.1-4.2_CHN Part 2 treatment emergent serious adverse events (TESAEs) during the double-blind epoch (regardless of study treatment relationship) - by primary system organ class, preferred term (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3.1-4.2 in CLCZ696B2319 RAP Section 14

Table 14.3.1-4.3_CHN Part 2 treatment emergent serious adverse events of special interest (TESAESIs) during the double-blind epoch - by risk category, preferred term (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3.1-4.3 in CLCZ696B2319 RAP Section 14

Table 14.3.1-7.2_CHN Part 2 study drug related treatment emergent adverse events (TEAEs) during the double-blind epoch - by primary system organ class, preferred term (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3.1-7.2 in CLCZ696B2319 RAP Section 14

Table 14.3.1-8.2_CHN Part 2 study drug related treatment emergent serious adverse events (TESAEs) during the double-blind epoch - by primary system organ class, preferred term (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3.1-8.2 in CLCZ696B2319 RAP Section 14

Table 14.3.1-9_CHN Part 2 study drug related treatment emergent adverse events of special interest TEAESIs) during the double-blind epoch - by risk category, preferred term (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3.1-9 in CLCZ696B2319 RAP Section 14

Table 14.3.1-10.1_CHN Part 2 treatment emergent adverse events (TEAEs) during the double-blind epoch, leading to permanent discontinuation of study treatment (regardless of study treatment relationship) - by primary system organ class, preferred term (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3.1-10.1 in CLCZ696B2319 RAP Section 14

Table 14.3.1-10.2_CHN Part 2 treatment emergent serious adverse events (TESAEs) during the double-blind epoch, leading to permanent discontinuation of study treatment (regardless of study treatment relationship) - by primary system organ class, preferred term (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3.1-10.2 in CLCZ696B2319 RAP Section 14

Table 14.3.1-10.3_CHN Part 2 treatment emergent adverse events of special interest (TEAESIs) during the double-blind epoch, leading to permanent discontinuation of study treatment (regardless of study treatment relationship) - by risk category, preferred term (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3.1-10.3 in CLCZ696B2319 RAP Section 14

Table 14.3.1-12.1_CHN Part 2 most common (>=1%) treatment emergent adverse events (TEAEs) during the double-blind epoch(regardless of study treatment relationship) - by primary system organ class, preferred term (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3.1-12.1 in CLCZ696B2319 RAP Section 14

Table 14.3.1-12.2_CHN Part 2 most common (>=1%) treatment emergent serious adverse events (TESAEs) during the double-blind epoch(regardless of study treatment relationship) - by primary system organ class, preferred term (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3.1-12.2 in CLCZ696B2319 RAP Section 14

Table 14.3.1-13.2_CHN Part 2 serum potassium related events - shift from baseline during the double-blind epoch (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3.1-13.2 in CLCZ696B2319 RAP Section 14

Table 14.3.1-14.2_CHN Part 2 hypotension related events during the double-blind epoch (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3.1-14.2 in CLCZ696B2319 RAP Section 14

Table 14.3.1-15.2_CHN Part 2 renal impairment related events during the double-blind epoch (baseline eGFR<=170) (Part 2 Safety Set: China Mainland Population)

Programming note: Refer to Table 14.3.1-15.2 in CLCZ696B2319 RAP Section 14

Table 14.3.1-15.3_CHN Part 2 renal impairment related events during the double-blind epoch(baseline eGFR>170) (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3.1-15.3 in CLCZ696B2319 RAP Section 14

Table 14.3.1-16.2_CHN Part 2 treatment emergent (newly occurring or worsening) adverse events (TEAEs) of positively adjudicated angioedema and angioedema-like event during the double-blind epoch by severity (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3.1-16.2 in CLCZ696B2319 RAP Section 14, without categorizing results by race

Table 14.3.1-19_CHN Part 2 treatment emergent (newly occurring or worsening) adverse events of special interest (TEAESIs) during the double-blind epoch, regardless of study treatment relationship - exposure adjusted incidence rate (EAIR) (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3.1-19 in CLCZ696B2319 RAP Section 14

Table 14.3.1-20_CHN Part 2 death during the double-blind epoch and primary cause of death (Part 2 Safety Set: China Mainland Population)
Programming note: Refer to Table 14.3.1-20 in CLCZ696B2319 RAP Section 14

4 Site specific report

For the site-specific reports, the list of significant adverse events for patients in China mainland will be needed for each site, which includes all of the following adverse events:

- Severe adverse events
- Adverse events leading to any change of study treatment or concomitant medications or non-drug therapy
- Adverse events linked to laboratory abnormalities

However, it is difficult to identify adverse events linked to laboratory abnormalities. Hence, the list of severe adverse events and adverse events leading to any change of study treatment or concomitant medications or non-drug therapy for patients in China mainland will be exported to a spreadsheet, and the rest adverse events for patients in China mainland will be exported to another spreadsheet. The adverse events linked to laboratory abnormalities need to be manually picked up.