Beijing Novartis Pharma Ltd.

A multicenter, interventional, open-label and single-arm study to investigate the effect of ARNI on ventricular arrhythmia in HFrEF patients with ICD or CRT-D

CLCZ696BCN04 / NCT04491136

Statistical Analysis Plan

Version: 1.0

Date: May 25, 2023

Approval Page of the Sponsor

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1.0	May 25, 2023	[redacted]	Final

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List of Abbreviations

Abbreviation	Explanation
ACEI	Angiotensin-converting enzyme inhibitor
AE	Adverse event
[redacted]	[redacted]
ALT	Alanine aminotransferase
ARB	Angiotensin receptor blockers
ARNI	Angiotensin receptor neprilysin inhibitor
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATP	Anti-tachycardia pacing
BID	Twice a day
BMI	Body mass index
BUN	Blood urea nitrogen
CPK	Creatinine phosphokinase
CRT-D	Cardiac resynchronization therapy-defibrillator
DLT	Dose limiting toxicity
DMP	Data management plan
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EOS	End of study
GCP	Good Clinical Practice
HF	Heart failure
HFrEF	Heart failure with ejection fraction decreased
ICD	Implantable cardioverter defibrillator
ICF	Informed consent form
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Milliliter(s)
NSVT	Non-sustained ventricular tachycardia
NT-proBNP	N-Terminal prohormone of Brain Natriuretic Peptide
NYHA	New York Heart Association
PVC	Premature ventricular contraction
QD	Once a day
QTcF	Fridericia QT correction formula
RBC	Red blood cell(s)
SAE	Serious adverse event
SAF	Safety set
SD	Standard deviation
SVT	Sustained ventricular tachycardia
TID	Three times a day
ULN	Upper limit of normal

VA	Ventricular arrhythmia
VT/VF	Ventricular tachycardia/fibrillation
WBC	White blood cell(s)
WHO	World Health Organization

1. Introduction

This Statistical Analysis Plan, prepared for "A multicenter, interventional, open-label and single-arm study to investigate the effect of ARNI on ventricular arrhythmia in HFrEF patients with ICD or CRT-D" (protocol number: CLCZ696BCN04) sponsored by Novartis, describes in detail the content and methods of statistical analysis.

This Statistical Analysis Plan is prepared based on the Study Protocol Version 02 dated March 15, 2022 and Case Report Form (CRF) Version 2.0 dated June 3, 2021.

2. Study Objectives

2.1 Primary Objective

The primary objective of this study is to assess the proportion of patients with VA events over 6 months of ACEI/ARB and 6 months of ARNI treatment.

2.2 Secondary Objectives

- To assess numbers of occurrences of VA events and ICD or CRT-D shocks over 6 months of ACEI/ARB and 6 months of ARNI treatment.
- To compare the changes in LVEF and NYHA level between ACEI/ARB and ARNI treatments
- To compare the changes in the NT-proBNP level between ACEI/ARB and ARNI treatments
- To compare the healthcare resource utilization of HF patients during ACEI/ARB and ARNI treatments

[redacted]

3. Study design

This will be a multicenter, interventional, open-label, and prospective single-arm study to evaluate the effect of ARNI on VAs in approximately 219 HFrEF patients receiving ICD or CRT-D in China.

After the informed consent process has been conducted and the patient has signed the informed consent form, baseline data will be collected. Implanted device data of patients will be collected for 12 months. ACEI/ARB therapy will be given to patients for 6 months. Dosage of ACEI/ARB will be based on investigator's discretion and up titrated after 2-4 weeks to the maximum dosage the patients can tolerate and according to product label.

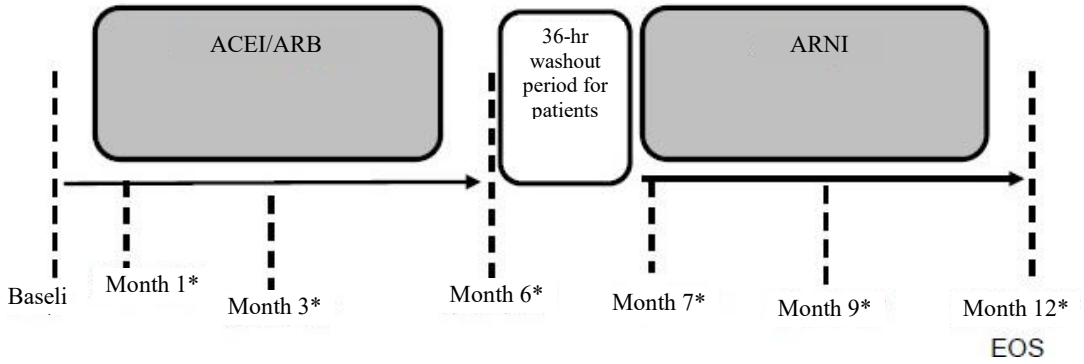
After 6 months, patients using ACEI need to undergo a 36-hr washout period (36-hr washout period is not needed for patients using ARB at month 6). Patients will then receive ARNI (sponsored by Novartis only for this study) while the dosage of ARNI will be according to investigator's discretion and up titrated to the maximum dosage the patient can tolerate or 200

mg bid as per guideline. Table 3-2 lists the recommended starting dose of ARNI.

All patients will be followed up for 6 months for each treatment. After patients finalize the trial, the investigator will evaluate all patients and produce a report.

Study flow chart:

Figure 3-1 Study design



Abbreviations: ACEI = Angiotensin-converting enzyme inhibitor; ARB = Angiotensin receptor blockers; ARNI = Angiotensin receptor neprilysin inhibitor; EOS = End of Study

Notes:

*Data collection at Baseline (0), Month 1, Month 3, Month 6, Month 7, Month 9, and Month 12 according to the evaluation schedule.

-Dosage and titration plan of ACEI/ARB and ARNI treatments will be according to investigator's discretion and product label (Please refer to Table 3-1 and Table 3-2).

-36-hr washout period is not needed for patients using ARB.

3.1 Patient numbering, treatment assignment, randomization

3.1.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No. eight-digit code), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. consists of the Center Number (Center No. four-digit code) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database.

3.1.2 Treatment assignment, randomization

This is a single-arm study, no treatment assignment will be involved in this study. No randomization will be performed in this study.

3.1.3 Treatment blinding

Treatment will be open to patients, investigator staff, persons performing the assessments, and the clinical trial team (CTT).

3.2 Sample Size Calculation

3.2.1 Primary endpoint

McNemar Test is used in the primary analysis to test for 2 correlated proportions. Approximate formula from Machin et al (1997) is used to calculate the minimum size required.

For the proportion of discordant pairs, the following approximate formula is used:

$$\text{Proportion Discordant} = P_t (1 - P_s) + P_s (1 - P_t)$$

where P_t and P_s are proportion of patients experiencing the event of interest during ACEI/ARB and ARNI treatment period respectively. Over here, both proportions are assumed to be similar to de Diego et al (2018)'s study. According to de Diego et al (2018)'s study, SVT (one of the VA event) has the following incidence 8/120 and 1/120 during ACEI/ARB and ARNI treatment period respectively. Hence, by substitute both into the equation above, proportion discordant calculated is 0.0739 after rounding off.

For the difference, a parameter under effect size is approximated by the following formula:

$$\text{Effect Size} = P_t (1 - P_s) + P_s (1 - P_t)$$

P_t and P_s after substituting Pt and Ps defined above, the effect size calculated is 0.0583.

Thus, by considering the parameters defined above, power of 0.8 and significance level of 0.05, the sample size required is 175. Further consider a dropout rate of 20%, the minimum sample size required is 219.

The above calculation is calculated using PASS 11 software's Test for Two Correlated Proportion (McNemar Test) [Differences] procedure.

For proportion of patients had ICD or CRT-D shocks occurrence over 6 months of ACEI/ARB and 6 months of ARNI treatment, the above sample size will provide 95% - 98% power to detect a proportion difference of 0.075 at two-sided significance level of 0.05. The proportion difference is derived from the published literature (de Diego et al 2018).

3.2.2 Power for analysis of selected secondary variables

The following test of secondary variables are part of the global testing strategy.

For the paired differences of numbers of NSVT, SVT, ICD shocks and ATP over ACEI/ARB and ARNI treatment period, the above sample size will provide >95% power to detect mean of paired difference of at least -3 and standard deviation of at most 10. These are under the assumption of similar patient experiences as de Diego et al (2018)'s study.

For the change from date of treatment initiation after 6 months of treatment assessed by LVEF and NT-proBNP, the above sample size will provide 84% – 91% power to detect a treatment difference of 3 numeric values at the two-sided significance level of 0.05, assuming a standard deviation of 15.

3.3 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are under investigator's discretion and according to product labels. Up-titration of patient's drug should

be according to the target dose or to the patient's maximum tolerance level.

3.3.1 Dose escalation guidelines

The dosage of ACEI/ARB and ARNI are under Investigator's discretion according to the recommended dosage (Yancy et al 2017) (Table 3-1). The recommended starting dose of ARNI for different population is presented in Table 3-2. If the patient is well tolerated, the dose of study drug should be up-titrated to next dose level until to target dose. Down-titration of the study drug at any time based on the judgment of the Investigator will be allowed with the consideration for patient safety and tolerability.

Table 3-1 Recommended dosage

Compound	Initial dose	Target dosage
ARNI (Sacubitril/Valsartan)	50 – 100 mg bid	200 mg bid
ACEI		
Enalapril	2.50 mg bid	10 mg bid
Captopril	6.25 mg tid	50 mg tid
Perindopril	2.00 mg qd	8 mg qd
Ramipril	1.25 mg qd	10 mg qd
Benazepril	2.5 mg qd	20 mg qd
ARB		
Candesartan	4 mg qd	32 mg qd
Valsartan	40 mg bid	160 mg bid
Losartan	25 – 50 mg qd	150 mg qd

Table 3-2 Recommended starting dose of ARNI

Population	Initial dose
Moderate or high-dose ACEI (equivalent of enalapril ≥ 10 mg bid)	100 mg bid
Moderate or high-dose ARB (equivalent of valsartan ≥ 80 mg bid)	100 mg bid
Low dose ACEI (equivalent of enalapril < 10 mg bid)	50 mg bid
Low dose ARB (equivalent of valsartan < 80 mg bid)	50 mg bid
Severe renal impairment (eGFR < 30 mL/min/1.73 m^2)	50 mg bid
Moderate hepatic impairment (Child-Pugh Class B)	50 mg bid
Elderly (age ≥ 75 years)	50 mg bid

3.3.2 Definitions of dose limiting toxicities

A dose limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs when taking study drugs. Dosage of study drugs is according to product label. Patients who meet any of the DLTs defined in the product label will be withdrawn from this study.

3.3.3 Dose modifications

Dose modifications are according to investigator's discretions and follow the local product label.

3.4 Interim analyses

The interim analysis (IA) and endpoint analysis will be performed in this study. An interim analysis will be performed when half of the required sample size (110 patients) have completed the 12-month treatment and follow-up period or prematurely withdrawn from study after at least one ARNI treatment, aiming at analyzing the study endpoints and safety, as well as re-evaluating the minimum sample size required.

For this interim analysis, the efficacy analysis will include efficacy data from 117 eligible subjects (i.e., subjects who have used ARNI at least once before freezing of the interim analysis data and completed the trial or early withdrawn).

Other analyses include all data from these 117 subjects and all subjects enrolled before these subjects.

4. Study Endpoints

4.1 Efficacy Endpoints

4.1.1 Primary endpoints

- **Assessment of ventricular arrhythmia events**

The proportion of subjects with VA events over 6 months of ACEI/ARB and 6 months of ARNI treatment will be statistically summarized.

Cardiac arrhythmia of ≥ 3 consecutive complexes originating in the ventricles at a rate > 100 bpm (cycle length: < 600 ms). Ventricular arrhythmia events that will be measured through device to determine SVT, NSVT and PVC:

1. Sustained ventricular tachycardia (SVT) is defined as tachycardia lasting for ≥ 30 seconds or with hemodynamic disorder as determined by Holter and/or device.
2. Non-sustained ventricular tachycardia (NSVT) is defined as recorded by Holter and/or device
3. Premature ventricular contraction (PVC) is defined as an early ventricular depolarization as determined by the device, and/or detected by Holter

- **Assessment of anti-tachycardia pacing and implantable cardioverter-defibrillator shocks**

The proportion of subjects with ATP, ICD, or CRT-D shocks over 6 months of ACEI/ARB and 6 months of ARNI treatment will be statistically summarized.

Once VA are detected, ICD can treat with high-energy shocks or ATP. ATP consists of one or more trains of pacing stimuli, expressed as a percentage of the tachycardia cycle length for a given RR interval, from the onset of the preceding R wave.

Subjects with sustained VA events will receive ICD or CRT-D shock therapy. Inappropriate shocks may occur in subjects with atrial fibrillation, SVT, or other intracardiac or extra cardiac signals. An inappropriate shock is defined as a shock not delivered for VT or VF and ending if sinus rhythm is redetected by the ICD. If a subsequent episode started within 5 minutes after the previous episode ended, it will be not considered as a new episode (van Rees et al 2011).

4.1.2 Secondary endpoints

- **Number of occurrences of VA**

The episodes of VA events over 6 months of ACEI/ARB and 6 months of ARNI treatment will be measured.

- **Left ventricular ejection fraction**

Left ventricular ejection fraction (%) will be compared at baseline, Month 6 and EOS.

- **NYHA level**

NYHA level will be recorded by investigators and compared at baseline, Month 6 and EOS.

- **NT-proBNP**

The measurements of NT-proBNP will be obtained from serum and plasma. Samples will be obtained before patients take their morning study drug dose. NT-proBNP (pg/mL) will be compared between ACEI/ARB and ARNI treatments at baseline, Month 6 and EOS.

- **Number of hospitalizations**

Number of hospitalizations for arrhythmia or HF related hospitalizations will be recorded during ACEI/ARB and ARNI treatments.

[redacted]

4.2 Safety Endpoints

4.2.1 Duration of exposure and exposure dose

In this study, detailed information such as date, time, dose and frequency of administration will be recorded in the CRF. The extent of exposure to ACEI/ARB and ARNI will be investigated, and the duration of exposure and planned and actual doses will be calculated.

Duration of exposure (days) = date of the last dose of the IMP - date of the first dose of the IMP + 1 If the subject's duration of drug exposure is discontinuous, the number of days without drug use will not be counted.

Total planned dose (mg) = total planned daily dose recorded in CRF * duration of exposure (days). Total actual dose (mg) = total actual daily dose recorded in CRF * duration of exposure (days).

4.2.2 Adverse Events

Adverse Events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

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

Treatment Emergent Adverse Event

A treatment emergent adverse event (TEAE) is an adverse event that occurs from the first dose of the study drug to 30 days after the last study treatment, or events occurring before the start of the treatment period and meeting any of the following three changes, as determined by the same preferred term (PT) under the same system organ class (SOC) based on MedDRA coding.

(1) Events which are present prior to the start of the treatment period but increased in severity;

(2) Events that change from being not suspected to being suspected of study drug relationship;

(3) Events that develop into SAEs after the start of the treatment period.

The increase in severity described above means that the same PT under the same SOC is present before the first administration of the investigational drug, but the severity of the PT during treatment is higher than the most severe grade before administration, or a new adverse event that occurs during treatment has a more severe grade (the same PT under the same SOC).

Severity is graded as mild, moderate and severe:

- Mild: usually transient in nature and generally not interfering with normal activities.
- Moderate: sufficiently discomforting to interfere with normal activities.
- Severe: prevents normal activities.

Treatment emergent adverse events will be counted for the specific treatment period. TEAEs in the ACEI/ARB treatment group refers to the adverse events that occur after the subject's

first ACEI/ARB administration and before ARNI administration. If the subject has not taken ARNI, TEAEs in the ACEI/ARB treatment group refer to adverse events that occur from the subject's first ACEI/ARB administration to 30 days after the subject's last ACEI/ARB administration. TEAEs in the ARNI treatment group refer to adverse events that occur from the subject's first ARNI administration to 30 days after the subject's last ARNI administration.

Pre-treatment events

Pre-treatment adverse events are defined as those that occur after the signing of the informed consent form and before the day of first administration of the investigational drug.

Drug-related adverse events (adverse reactions)

An adverse drug reaction (ADR) is a toxic and adverse reaction to a drug. An ADR indicates that there is at least a reasonable likelihood of a causality between the drug and an adverse event. In this study, the causality between an adverse event and the investigational drug is judged according to "suspected" and "not suspected". "Suspected" adverse events are judged as adverse reactions. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication), the assessment of causality will usually be 'Not suspected.'

AEs leading to death

Adverse events leading to death will be recorded by the investigator on the CRF Adverse Events Form. In addition, there is a specialized CRF to record deaths.

Serious adverse events

SAEs will be collected between time patient signs ICF until 30 days after the patient has discontinued or stopped study treatment. An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of an SAE refers to a reaction in which the patient is at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it is more severe.

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.

- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent.
- social reasons and respite care in the absence of any deterioration in the patient's general condition.
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission.

- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such medical events are: allergic bronchospasm that requires intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that did not lead to hospitalization or development of dependency or abuse.

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

All reports of intentional misuse and abuse of the product are also considered SAE irrespective if a clinical event has occurred. Serious adverse events will be determined by the investigator on the original document or certified copy and entered into the CRF.

Adverse events leading to permanent discontinuation

In the study, action taken with study drug is drug discontinued or the subject will be withdrawn from treatment in response to these AEs.

4.2.3 Laboratory test

It will be done at the study site according to the laboratory requirements and standards of the study site. Laboratory tests include hematology, blood biochemistry, kidney function, biomarkers, and pregnancy tests.

Category	Items
Hematology	Red blood cells count, white blood cells count, platelet count, hemoglobin, hematocrit, and WBC differential
Blood chemistry	Potassium, creatinine, glucose, sodium, chloride, calcium, blood urea nitrogen, total bilirubin, fractionated bilirubin (if total bilirubin >2x ULN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total protein, albumin, uric acid, cholesterol, triglyceride, low density lipoprotein, high density lipoprotein, eGFR,

	glycosylated haemoglobin
Kidney function	Serum creatinine
Biomarkers	NT-proBNP
Pregnancy test	Serum/urine pregnancy test

4.2.4 12-lead ECG examination

The CRF collects the test results of heart rate, RR interval, PR interval, QT interval, QRS interval and QTcF interval and their clinical assessments (normal, abnormal with no clinical significance, abnormal with clinical significance).

4.2.5 Holter

The CRF collects the results of ventricular premature beat, atrial premature beat, mean heart rate, ventricular tachycardia, and atrial tachycardia.

4.2.6 Echocardiography

The CRF collects the test results of left ventricular ejection fraction (LVEF) (%) and left ventricular end-diastolic diameter (LVEDD) (mm).

4.2.7 Vital signs

The CRF collects subjects' mean systolic blood pressure, mean diastolic blood pressure, body temperature, heart rate, and respiratory rate measurements and their clinical assessments (normal, abnormal with no clinical significance, abnormal with clinical significance).

4.2.8 Physical examination

The CRF collects subjects' skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, limbs, blood vessels, nervous system, rectum, external genitalia, breasts, pelvis, and other examinations and their clinical assessments (normal, abnormal with no clinical significance, abnormal with clinical significance).

4.2.9 Pregnancy test (only for women of childbearing)

The CRF collects subjects' (women of reproductive age) blood and urine pregnancy test results.

4.3 Demographics and Disease Characteristics

The CRF collects subjects' date of birth, age, gender, ethnicity, height, weight, and BMI.

The CRF collects current and past medical history, and history of heart failure.

4.4 Past and concomitant medication and concurrent treatment

The CRF collects the drug name, total daily dose and unit, frequency of administration, route of administration, start date, end date, ongoing or not, and indication for prior and concomitant medications.

The CRF collects the name, start date, end date, ongoing or not, and indication of concomitant treatments (non-drug concomitant treatments, including surgery).

4.5 Protocol Deviation and Medication Compliance

Protocol deviations will be recorded by the clinical monitor.

Medication compliance for ACEI/ARB and ARNI is defined as: total actual dose/total planned dose *100%. Overall medication compliance for ACEI/ARB and ARNI will be summarized.

5. Statistical Hypotheses

For details, see section 7.4 Efficacy Analysis.

6. Analysis Datasets

The analysis data sets of this study are as follows.

Screened set

It includes all subjects who have signed the informed consent form.

Safety Analysis Set, SS

It includes all subjects who had received at least one dose of study treatment. Analyses will be performed according to the study treatment received. The safety analysis set will be used for all analyses except the efficacy analysis.

Efficacy Analysis Set

It includes SS subjects who have received ARNI at least once and completed 12 months of complete treatment and follow-up or who have early withdrawn from the study after receiving ARNI at least once. The efficacy analysis set will be used as the primary population to analyze the efficacy variables.

Per Protocol Set, PPS

It includes subjects in efficacy analysis set who had no major protocol violations, and the PP population will be used for efficacy analysis.

7. Statistical Methods

7.1 Overall Statistical Considerations

All statistical analyses are performed using SAS9.4.

All subjects related, efficacy related and safety related data should be collected and included in the statistical analysis. Notes or descriptive text records are only listed. For other data, descriptive statistical analysis would be performed, also statistical inference would be applied if needed.

In the statistical tabulations, screening number of subjects is the universal unique identifier of subjects in the study.

General rules of descriptive statistics: Quantitative variables are described by mean, standard deviation, standard error, median, minimum, maximum, Q1 and Q3. Categorical variables are

described by number and percentage of each category. Two-sided 95% confidence intervals will also be calculated for efficacy endpoints.

In the laboratory test part and the efficacy analysis part, 2 digits will be retained for the upper and lower limits of means and their confidence intervals, 3 digits for standard deviations, and 2 digits for medians, minimums, maximums, Q1 and Q3. In other parts, 1 digit more than the original values can be retained for the upper and lower limits of means and their confidence intervals, 2 digits more for standard deviations, and the original value digits for medians, minimums, maximums, Q1 and Q3. One decimal place will be retained for percentages and the upper and lower limits of their confidence intervals (but for efficacy analysis, 2 decimal places will be retained).

General principles of statistical inference: paired t test and Wilcoxon rank sum test will be used to compare quantitative data. McNemar test, exact test (binomial sign test) and Liddell's exact test will be used to compare categorical variables. All statistical tests will be subjected to two-sided tests (unless otherwise specified), and a P-value less than or equal to 0.05 will be considered to indicate a statistically significant difference (unless otherwise specified).

For values such as "< xxx", half of the number following the less-than sign will be used to summarize and calculate statistics. For values such as "> xxx", xxx will be used to summarize and calculate statistics. For values such as "xx-xx", the average of the numbers before and after "-" will be used to summarize and calculate statistics. P value is rounded to 4 decimal places. If P < 0.0001, it is presented as '< .0001'; if P > 0.9999, it is presented as '> .9999'.

Baseline definition: Visit 1 data will be used as baseline of ACEI/ARB, and Visit 4 data as baseline of ARNI. If Visit 4 data are missing, the last available data before Visit 4 will be used.

Unless otherwise specified, the statistical description by visit only included the data of scheduled visits. For the evaluation involving maximum change, minimum change, abnormality, and clinically significant findings, the data of scheduled visits and unscheduled visits should be included.

Adverse events and medical history will be coded using MedDRA (see DMP for the specific version number).

Prior medications and concomitant medications will be coded using WHO Drug Dictionary (see DMP for the specific version number).

7.2 Methods for Data Processing

7.2.1 Early withdrawal and missing data

No missing data will be imputed unless otherwise specified. In case of missing categorical data, it will be listed as a missing item. Missing dates for concomitant medications and adverse events (AEs) will be imputed.

Missing dates for concomitant medications will be imputed as follows. Missing dates for

concomitant medications will be imputed only to judge the classification (prior/concomitant), and the list still shows unimputed dates.

- Starting date of concomitant medication is missing
    1) If the year and month are known, the missing day will be imputed as the first day of the corresponding month.
    2) If only the year is known, the missing month and day will be imputed as January 1.
- The end date of concomitant medications is missing
    1) If the year and month are known, the missing day will be imputed as the last day of the corresponding month.
    2) If only the year is known, the missing month and day will be imputed as 31 December.

The imputed start date of the concomitant medication should not be earlier than the subject's date of birth, and the imputed end date should not be later than the subject's date of death. The imputed start date of the concomitant medication should be earlier than or equal to the end date of the concomitant medication.

Missing dates of AEs are imputed as follows: missing dates of AE are imputed for the purpose of AE classification only, and unimputed dates are still displayed when AE-related data listings will be generated.

- Missing of start date of AE
    1) If the year and month are known and both are earlier than those of the first dose of the investigational drug, the last day of the known month will be used for imputation.
    2) If the year and month are known and equal to the year and month of the first administration of the investigational drug, and the end date is missing or equal to or later than the date of the first administration of the investigational drug, the start date of the AE should be equal to the date of the first administration of the investigational drug [date means "xx xx (month day)"]; if the end date is earlier than the date of first administration of the investigational drug, the first day of the known month will be used for imputation.
    3) If the year and month are known and later than those of the first dose of the investigational drug, it will be imputed with the first day of the known month.
    4) If only the year is known and earlier than that of the first dose of the investigational drug, "December 31" will be used for imputation.
    5) If only the year is known and same as that of the first dose of the investigational

drug, and the end date is missing or the same as or later than the date of the first dose, the start date of AE is the date of the first dose of the investigational drug (date refers to "month, day").

6) If only the year is known and later than that of the first dose of the investigational drug, it will be imputed with "January 1".

7) If the year, month, and day are all missing, and the end date is missing or equal to or later than the date of first administration of the investigational drug, the date of first administration of the investigational drug will be used as the corresponding start date.

8) Other conditions are regarded as missing.

- Missing of end date of AE

1) If the year and month are known, it will be imputed with the last day of the known month.

2) If only the year is known, it will be imputed with "December 31".

3) Other conditions are regarded as missing.

The imputed AE start date should not be earlier than the subject's date of birth, and the imputed AE end date should not be later than the subject's date of death. The imputed AE end date should be later than or equal to the AE start date.

7.2.2 Derived and converted data

Except for the calculation of certain study endpoints based on the data collected from CRF, no other data are derived or converted. For outliers, data queries are reported to the DM and solved or verified before database lock. No special data processing is performed.

7.3 Study Subjects

7.3.1 Subject disposition

The number of subjects who had signed the informed consent form but not enrolled are calculated, making the distinction between screen failures and subjects who do not fail screening but are not enrolled. Screen failures and subjects who did not fail screening but are not enrolled are listed, providing the reasons.

Based on safety analysis set, the number and percentage of subjects who had completed and early withdrawn from the study are calculated, as well as the number and percentage of subjects who early withdrew due to various reasons. Reasons for early withdrawal are listed.

7.3.2 Protocol deviations

Based on the safety analysis set, details of subjects with major protocol deviations should be listed.

7.3.3 Analysis datasets

Based on the safety analysis set, the number and percentage of subjects included in the efficacy analysis set and per protocol set will be calculated. Reasons for non-inclusion are listed.

7.3.4 Demographics and baseline characteristics

The analysis is performed based on the SS.

The age, sex, ethnicity, height, weight, BMI, and other demographic data are statistically described. Past medical history, history of present illness, history of heart failure and NYHA classification will be statistically described.

Demographic data, past medical history, history of present illness, history of heart failure, and NYHA classification will be listed.

7.3.5 Prior and concomitant medications and therapies

The analysis is performed based on the SS.

The duration of non-investigational drug use will be compared with the duration of study drug use, and non-investigational drug use will be divided into prior and concomitant medications.

Prior medication refers to a non-investigational drug that is started and ended before the first dose of study drug. Concomitant medication refers to a non-investigational drug that meets one of the following conditions:

1) Starting at or after the first dose of the investigational drug
2) Starting before the first dose of the investigational drug and continuing at or after the first dose of the investigational drug.

The number and percentage of subjects using various drugs will be calculated for prior and concomitant medications respectively. The prior and concomitant medications will be listed.

Concomitant treatments (including all non-drug concomitant treatments such as surgery) will be listed.

7.3.6 Treatment compliance

The analysis is performed based on the SS.

The study drug compliance will be described statistically as a quantitative variable.

7.4 Efficacy Analysis

7.4.1 Efficacy analysis of primary endpoint

The analysis will be based on the efficacy analysis set and the per protocol set.

- Proportion of paired patients who developed at least one SVT over 6 months of ACEI/ARB and 6 months of ARNI treatment.
- Paired proportion of patients by the occurrence of at least one NSVT over 6 months of ACEI/ARB and 6 months of ARNI treatment.
- Paired proportion of patients by the occurrence of at least one PVC over 6 months of ACEI/ARB and 6 months of ARNI treatment.
- Paired proportion of patients by the occurrence of at least one ICD or CRT-D shock over 6 months of ACEI/ARB and 6 months of ARNI treatment.
- Paired proportion of patients by the occurrence of at least one ATP event over 6 months of ACEI/ARB and 6 months of ARNI treatment.

Different hypothesis testing will be done on different types of variables:

Analysis of paired patient proportion

Occurrence events to be considered are SVT, NSVT, PVC, ICD or CRT-D shocks and ATP.

For each of the occurrence event, number of patients with at least one event stratified by treatments, will be presented in a 2 × 2 contingency table as follow:

Table 5-1 Matched pairs 2 × 2 contingency table

ARNI (case)	ACEI/ARB (control)		
	At least one event	No event	Total
At least one event	a	b	$a + b$
No event	c	d	$c + d$
Total	$a + c$	$b + d$	$N = a + b + c + d$

The following statistical hypothesis under 95% significance level will be tested to address the primary objective:

Null hypothesis: $p_b = p_c$ versus alternative hypothesis: $p_b \neq p_c$, where p_b and p_c are b/N and c/N, respectively. The test statistic considered is McNemar Test statistic as follow:

$$\chi^2 = \frac{(b-c)^2}{b+c}$$

which has a chi-squared distribution with degree of freedom of one.

However, an exact test (binomial sign test) will be used if the discordant cells have low values (b +c < 25).

Supportive analyses

In addition to the primary analysis, all the paired proportion will also be analyzed using the Liddell's exact test (Liddell 1983) as supportive analysis. From Table 5-1, the maximum likelihood estimate of relative risk (Mantel and Haenszel 1959), $\widehat{R}$ is given as follow:

$$\widehat{R} = \frac{b}{c}$$

Null hypothesis:$\widehat{R} = 1$ versus alternative hypothesis: $\widehat{R} \neq 1$ The test statistic considered, F is given as follow:

$$F = \frac{b}{c+1}$$

which has a F-distribution with degrees of freedom of 2(c+1) and 2b. Two-sided probability and 95% confidence interval of estimated relative risk will be presented as well.

For all primary endpoints, the proportion of patients with at least one event over 3 months of ACEI/ARB and 3 months of ARNI treatment will be analyzed.

7.4.2 Efficacy analysis of secondary endpoints

The analysis will be based on the efficacy analysis set and the per protocol set.

- Paired numbers of VA (SVT and NSVT in separate), PVC, ICD or CRT-D shocks and ATP over 6 months of ACEI/ARB treatment and 6 months of ARNI treatment.
- Change in LVEF from date of treatment initiation over 6 months of ACEI/ARB treatment and 6 months of ARNI treatment.
- Change of NYHA level over 6 months of ACEI/ARB treatment and 6 months of ARNI treatment.
- Change proportion of NT-proBNP from date of treatment initiation over 6 months of ACEI/ARB treatment and 6 months of ARNI treatment.
- Number of hospitalizations for all causes and HF related hospitalizations during ACEI/ARB and ARNI treatments.
- Paired numbers of VA (SVT and NSVT in separate), PVC, ICD or CRT-D shocks and ATP over 3 months of ACEI/ARB treatment and 3 months of ARNI treatment.
- Number of hospitalizations for all causes and HF related hospitalizations during 3 months of ACEI/ARB and ARNI treatments.

Analysis of change from date of treatment initiation after 6 months of treatment (for paired quantitative endpoints)

Variables involved are number of SVT experienced, number of NSVT experienced, number of hourly PVC experienced, number of ICD or CRT-D shocks experienced, number of ATP experienced and time duration of NSVT experienced, as well as number of hospitalizations for

all causes and HF related hospitalizations.

The number of occurrences or duration of each variable within 3 months and 6 months and their changes from baseline will be descriptively analyzed by treatment group and compared between groups. The changes will be summarized by mean, standard error, median, quartiles, minimum and maximum. Because the baseline and post-treatment device data collection cycles are different, data will be standardized on a daily basis before the analysis of changes.

Normality will be checked for the values of each variable and changes calculated. If the data is parametric, paired t-tests will be performed; else if the data is non-parametric, Wilcoxon signed-rank test will be used.

Analysis of change from date of treatment initiation after 6 months of treatment (for continuous endpoints)

Variables involved are LVEF, NYHA and NT-proBNP.

The values of each variable at visits following 3 months and 6 months of treatment and their changes from baseline will be descriptively analyzed by treatment group and compared between groups. The changes will be summarized by mean, standard error, median, quartiles, minimum and maximum.

Normality will be checked for the values of each variable and changes calculated. If the data is parametric, paired t-tests will be performed; else if the data is non-parametric, Wilcoxon signed-rank test will be used.

NYHA is a qualitative variable, and NYHA level will be subject to Ridit transformation into a numerical Ridit value before the above analysis is carried out. The basic idea of Ridit transformation is to first determine a standard group (the sum of the frequencies of each treatment group of each grade is taken as the standard group), and then obtain the Ridit value R of each grade of the standard group. The weighted average of the frequency of each grade in each group and the R value of each grade in the standard group will be respectively used to obtain the average Ridit value of each group, and then compare between groups.

7.5 Safety Analysis

7.5.1 Drug exposure

The analysis is performed based on the SS.

The exposure to the study drug (duration of exposure, total planned dose, total actual dose) will be statistically described and summarized by treatment group and by mean, standard deviation, median, minimum, and maximum.

The number and percentage of patients in each treatment group will be summarized for duration of exposure in the following groups.

- < 30 days
- 30 days <= duration of exposure <60 days
- 60 days <= duration of exposure <90 days
- 90 days <= duration of exposure <120 days
- 120 days <= duration of exposure <150 days
- 150 days <= duration of exposure <180 days
- Duration of exposure >=180 days

7.5.2 Adverse events

The analysis is performed based on the SS. The safety summary only analyzes data during

treatment.

The overall occurrence of adverse events during treatment will be summarized by treatment group, and the overall incidence of adverse events during various treatment periods will be calculated. The number and percentage (%) of subjects (n) with treatment emergent adverse events, treatment emergent serious adverse events, drug-related treatment emergent adverse events, treatment emergent adverse events leading to withdrawal from treatment, and treatment emergent adverse events leading to death will be summarized. A separate summary of deaths will also be provided, including the number of deaths during and after treatment. Upon calculating the frequency and percentage of subjects that experienced adverse events, if a subject developed multiple adverse events in the same classification, it would be counted once.

Among treatment emergent adverse events, the number (n) and percentage (%) of subjects with various adverse events by system organ class (SOC) and preferred term (PT) thereunder will be calculated by each treatment group. These include treatment emergent adverse events, serious adverse events, drug-related adverse events, and adverse events leading to withdrawal from treatment. For the calculation of the number and percentage of subjects, if a subject had multiple adverse events of the same SOC and PT, only one event will be counted.

Among treatment emergent adverse events, the incidence (number and percentage of subjects) of various treatment emergent adverse events and drug-related adverse events will be calculated by system organ class (SOC), preferred term (PT), and severity (mild, moderate, severe). If a subject had multiple adverse events with the same preferred term, such event is counted only once within such preferred term, and the event with the highest severity is counted.

System organ class (SOC) and/or preferred term (PT) will be presented in a descending order of incidence in the ARNI treatment group and incidence in the ACEI/ARB treatment group.

All adverse events, serious adverse events, and adverse events leading to withdrawal from treatment will be listed separately. A detailed list describing details of subject deaths will be provided.

7.5.3 Laboratory test results

The analysis is performed based on the SS.

From baseline, the quantitative laboratory tests results of each visit and their changes from baseline will be calculated and summarized in descriptive statistics. Pre-treatment and post-treatment laboratory test results are classified into abnormal with clinical significance, abnormal with no clinical significance, normal and not tested in an order of abnormal with clinical significance > abnormal with no clinical significance > normal > not tested, and then a shift table will be generated.

The listing for all abnormal findings in laboratory data will be provided.

7.5.4 12-lead ECG

The analysis is performed based on the SS.

The 12-lead ECG results and their changes from baseline are statistically described by visit.

The pre-treatment and post-treatment ECG results are classified in the order of abnormal with clinical significance, abnormal with no clinical significance, normal, not examined, and then a shift table will be generated.

12-Lead ECG results of all subjects will be listed.

7.5.5 Holter

The analysis will be performed based on the SS.

The quantitative Holter results and their changes from baseline will be statistically described by visit. All Holter results will be tabulated in detail.

7.5.6 Echocardiogram

The analysis will be performed based on the SS.

The echocardiogram results and their changes from baseline will be statistically described by visit. The pre-treatment echocardiogram results and post-treatment echocardiogram results will be classified in the order of abnormal with clinical significance, abnormal with no clinical significance, normal, not examined, and then a shift table will be generated.

All echocardiogram results will be listed.

7.5.7 Vital signs

The analysis will be performed based on the SS.

From baseline, the mean systolic blood pressure, mean diastolic blood pressure, body temperature, heart rate and respiratory rate at each visit and their changes from baseline will be statistically described.

The pre-treatment vital sign results and post-treatment vital sign results will be classified into abnormal with clinical significance, abnormal with no clinical significance, normal and not tested in an order of abnormal with clinical significance > abnormal with no clinical significance > normal > not tested, and then a shift table will be generated.

All vital sign results will be tabulated.

7.5.8 Physical examination

The analysis will be performed based on the SS.

All physical examination results will be tabulated.

7.5.9 Pregnancy test

The analysis will be performed based on the SS.

All pregnancy test results will be tabulated.

8. References

(1) Guidelines on Biostatistics in Clinical Trials

(2) Guidelines on Planning and Reporting of Clinical Trial Data Management and Statistical Analysis

(3) CLCZ696BCN04_Protocol_01_20200508_CN.pdf

(4) CLCZ696BCN04_Protocol_02_Clean Version_CN.pdf

9. Templates of Statistical Figures and Tables

Details are provided in separate documents CLCZ696BCN04 Mock-up Shell_V1.0.rtf and CLCZ696BCN04 Mock-up Shell_16.2 listing_V1.0.docx