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LCZ696

Clinical Trial Protocol CLCZ696BCN04 / NCT04491136

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

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List of abbreviations

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
AT_1	Angiotensin II type 1
ATC	Anatomical Therapeutic Chemical
ATP	Anti-tachycardia pacing
b.i.d.	bis in die/twice a day
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CMO & PS	Chief Medical Office and Patient Safety
CO	Country Organization
CPK	Creatinine phosphokinase
CRO	Contract Research Organization
CRT-D	Cardiac resynchronization therapy-defibrillator
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose limiting toxicity
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EOS	End of study
ePRO	Electronic patient reported outcome
eSource	Electronic Source
FAS	Full Analysis Set
GCP	Good Clinical Practice
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
hr	hour
ICD	Implantable cardioverter defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
LVEF	Left ventricular ejection fraction
MedDRA	Medical dictionary for regulatory activities

[redacted]

mg	milligram(s)
mL	milliliter(s)
NEP	Neutral endopeptidase
NSVT	Non-sustained ventricular tachycardia
NT-proBNP	N-Terminal prohormone of Brain Natriuretic Peptide
NYHA	New York Heart Association
PARADIGM-HF	The prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor with an Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure
p.o.	oral(ly)
PVC	Premature ventricular contraction
QD	Once a day
QMS	Quality Management System
QTcF	Fridericia QT correction formula
RBC	Red blood cell(s)
SAE	Serious Adverse Event
SAF	Safety Set
SD	Standard deviation
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVT	Sustained ventricular tachycardia
ULN	Upper limit of normal
VA	Ventricular arrhythmia
VT/VF	Ventricular tachycardia/fibrillation
WBC	White blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), urine, etc. taken from a patient.
Cohort	A specific group of patients fulfilling certain criteria and generally treated at the same time.
Control drug	A study intervention (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day).
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last patient or at a later point in time as defined by the protocol.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained.
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study.
Medication number	A unique identifier on the label of medication kits.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy).
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest for the study.
Patient number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis.

[redacted]

Personal data	Patient information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes patient identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized patient.
Run-in Failure	A patient who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to patient's intervention or other treatment).
Screen Failure	A patient who did not meet one or more criteria that were required for participation in the study.
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first patient.
Study treatment	Any drug or combination of drugs or intervention administered to the patients as part of the required study procedures; includes investigational drug(s) or control(s).
Study treatment discontinuation	When the patient permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each patient that is required to address the clinical question. The specification of the variable might include whether the patient experiences an intercurrent event.
Withdrawal of consent	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

[redacted]

Amendment 2 (Feb 2022)

Amendment rationale

Study was initiated in 19-Oct-2020. As of 31-Jan-2022, a total of 142 patients have been enrolled in the study. The slow enrollment of patients was impacted by the COVID-19 pandemic. This amendment is aimed to reduce the study sample size by modification of the statistical power of sample size calculation.

Changes in the protocol

Chapter	V01	V02	Reason
Protocol summary (Study design), Section 3, Section 5	275 HFrEF patients	219 HFrEF patients	Sample size is updated
Protocol summary – Exclusion criteria	2. Patients who received ARNI within 6 weeks prior to study	2. Patient received target dose (≥200 mg/d) of ARNI for 2 weeks continuously within the 6-week period prior to study enrollment.	Define 6-week period
Section 4.4	NA	In the event of a public health emergency as declared by local or regional authorities (i.e., pandemic, epidemic or natural disaster), mitigation procedures may be required to ensure participant safety and trial integrity and are listed in relevant sections of the study protocol. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by local or regional health authorities and ethics committees as appropriate.	New section: COVID-19-related information is added
Section 4.5, Section 12.7	138 patients	110 patients	Sample size for interim analysis is updated
Section 4.6	NA	In the context of COVID-19 pandemic, there is still lack of evidence about the risks or benefits of ARNI and ACEI/ARB in COVID-19 patients.	COVID-19-related information is added
Section 5.2	2. Patients who received ARNI within 6 weeks prior to study	2. Patient received target dose (≥200 mg/d) of ARNI for 2 weeks continuously within the 6-week period prior to study enrollment.	Exclusion criterion 2 is updated to define 6-week period

[redacted]

Chapter	V01	V02	Reason
Section 6.5.1 – Table 6-3	Moderate or high-dose ARB (equivalent of valsartan 10 mg bid)	Moderate or high-dose ARB (equivalent of valsartan ≥80 mg bid)	Error
Section 6.7	NA	During the COVID-19 pandemic in which on-site study visits may be impacted, delivery of study treatment directly to a patient's home is generally permitted. If delivery is not available, patients may purchase the study drugs themselves. Patients will be reimbursed for the study drug cost with drug packaging as proof of purchase.	COVID-19-related information is added
Section 6.9	NA	In the event of an overdose, the Investigator should: • Contact the medical monitor immediately. • Evaluate the patient to determine, in consultation with the medical monitor, whether study treatment should be interrupted or whether the dose should be reduced. • Closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 30 days. • Document the quantity of the excess dose as well as the duration of the overdose.	Information about overdose are added.
Section 6.9.1	NA	Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition). Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol. Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.	Information about misuse/abuse are added

[redacted]

Chapter	V01	V02	Reason
		Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness. For more information on AE and SAE definition and reporting requirements, please see the respective sections.	
Section 7	NA	In the event of recollection of informed consent is needed, the Investigator may conduct the informed consent discussion remotely (e.g., telephone or video conference). Guidance issued by local regulatory bodies, and ECs/IRBs on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).	Remote consent for recollection of informed consent is added.
Section 8.5	every 3-6 month through this study	when necessary	No meeting held by review committee since the study initiated
Section 12.8	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.	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.	Reduce the study sample size by reducing the statistical power

Minor edits and corrections of typos are also made throughout the protocol. Several updates are also made according to the wordings in CTP template V5.0.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval.

[redacted]

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 1 (May 2020)

Study protocol amendments and updates (from V00 to V01) are based on launch meeting, especially inclusion and exclusion criteria, as this is more reasonable and executable in investigator practices.

Chapter	V00	V01	Reason
Protocol summary-Key Inclusion criteria 5.1 Inclusion criteria	2. Implanted with an ICD or CRT-D within 1 week	2. Implanted with an ICD or CRT-D within 2 weeks	Reasonable criteria in clinical practice
Protocol summary-Key Exclusion criteria 5.2 Exclusion criteria	2. Patients who received ARNI within 2 months prior to study enrollment	2. Patients who received ARNI within 6 weeks prior to study enrollment	Reasonable criteria in clinical practice
Protocol summary-Key Exclusion criteria 5.2 Exclusion criteria	8. Symptomatic hypotension < 90/60 mmHg in anti-hypotension drug treatment at Visit 1 (screening)	8. Symptomatic hypotension < 90/60 mmHg in anti-hypertension drug treatment at Visit 1 (screening)	Wording error
[redacted]	[redacted]	[redacted]	[redacted]
4.2 Rationale for dose/regimen and duration of treatment	ACEI is recommended by treatment guidelines as the treatment of choice for HFrEF patients	ACEI/ARB is recommended by treatment guidelines as the treatment of choice for HFrEF patients	Wording error
5.2 Exclusion criteria	11.Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test (> 5 mIU/mL).	11.Pregnant or nursing (lactating) women	Delete extra description
6.1.1 Investigational and control drugs		Basically, initiated ARNI dosage accord to ACEI/ARB alternative dosage, but investigators have discretion to prescribe ARNI dosage	Add initial dosage of ARNI.

[redacted]

Chapter	V00	V01	Reason
6.2.1 Concomitant therapy		Amiodarone dosage must be consistent for patient treatment during this study, if radiofrequency ablation is necessary, the patient should withdraw from the study.	Definition the dosage of Amiodarone in special case.
6.2.3 Rescue medication	Any patient who experiences a potassium level ≥6.0 mmol/L confirmed by repeated same blood sample testing should be withdrawn from the study treatment.	Any patient who experiences a potassium level >6.0 mmol/L confirmed by repeated same blood sample testing should be discontinued from the study treatment.	Clarify hyperkalemia is not imply the patient will quit the study forever if effective treatment.
9.1.1 Study treatment discontinuation and study discontinuation	4. Serum potassium >6.0 mmol/L at follow Visit	“Serum potassium >6.0 mmol/L at follow Visit” is moved from “Study treatment must be discontinued under the following circumstances” to “Study medication may be discontinued at the investigator’s discretion if any of the following occurs”	Avoid study treatment discontinuation result of transient hyperkalemia

[redacted]

Protocol summary

Protocol number	CLCZ696BCN04
Full Title	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
Brief title	RHYTHM
Sponsor and Clinical Phase	Novartis Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to generate effectiveness data of ARNI, in the Chinese HFrEF patients with implanted ICD or CRT-D. The rationale of this study is to compare the effect of ACEI/ARB with the effect of ARNI on VA events for HFrEF patients with ICD or CRT-D, thus a multicenter, interventional, open-label, and prospective single-arm study was considered.
Primary Objectives	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
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]	[redacted]
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 patient is informed and asked to sign an informed consent form, baseline data will be collected. Device data of patients will be collected for 12 months. ACEI/ARB will be given to the patient 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. 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. An interim analysis is planned when half of the required sample size (110 patients) have completed the study. The intent of the interim analysis is to

[redacted]

	stop for futility or high incidence of safety events and re-evaluate minimum sample size required.
Study population	The study population will consist of approximately 219 patients with HFrEF (LVEF ≤40%) in around 25 sites, aged between 18 years and 80 years, implanted with ICD/CRT-D devices.
Key Inclusion criteria	1. Male or female patients ≥18 and ≤80 years of age 2. Implanted with an ICD or CRT-D within 2 weeks 3. NYHA functional class II – IV 4. LVEF ≤40% (measured by echocardiography) 5. Signed informed consent must be obtained prior to participation in the study.
Key Exclusion criteria	1. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes. 2. Patient received target dose (≥200 mg/d) of ARNI for 2 weeks continuously within the 6-week period prior to study enrollment. 3. Participation in other clinical studies 3 months prior to participating study 4. Advanced cancer or other significant comorbidities with life expectancy of <1 year 5. Previous history of angioedema associated with ACEI/ARB treatment, hereditary or idiopathic angioedema 6. Patients with renal artery stenosis history 7. Current stage D HF patients requiring vasoactive drugs 8. Symptomatic hypotension < 100/60 mmHg at visit 1 (screening) or Symptomatic hypotension < 90/60 mmHg in anti-hypertension drug treatment at visit 1 (screening) 9. Serum potassium >5.4 mmol/L at visit 1 (screening) 10. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 as measured at visit 1 (screening) 11. Pregnant or nursing (lactating) women 12. Other exclusion depend on investigator's discretion
Study treatment	Patients will receive ACEI/ARB, where generics are acceptable. Patients will receive then ARNI treatment for 6 months.
Treatment of interest	Patients will receive ACEI/ARB for 6 months and then ARNI for 6 months. Patients will initiate ARNI treatment after a 36-hr washout period after the ACEI treatment.
Efficacy assessments	**Primary efficacy endpoints** 1. The proportion of patients with VA events over 6 months of ACEI/ARB and 6 months of ARNI treatment will be measured. 2. Proportion of patients had ATP, ICD or CRT-D shocks occurrence over 6 months of ACEI/ARB and 6 months of ARNI treatment will be measured. **Secondary efficacy endpoints** 1. The episodes of VA events over 6 months of ACEI/ARB and 6 months of ARNI treatment will be measured. 2. LVEF (%) will be compared at baseline, Month 6 and EOS. 3. NYHA level will be recorded by investigators and compared at baseline, Month 6 and EOS. 4. The measurements of NT-proBNP will be obtained from serum or plasma. Samples will be obtained before patients take their morning study drug

[redacted]

	dose. NT-proBNP (pg/mL) will be compared between ACEI/ARB and ARNI treatments at baseline, Month 6 and EOS. 5. Number of hospitalizations for arrhythmia or HF related hospitalizations will be recorded during ACEI/ARB and ARNI treatments. [redacted]
Key safety assessments	Adverse event monitoring, physical examinations, vital signs, height and weight, laboratory evaluations, ECG, and pregnancy test.
Data analysis	Enrolled Set: all patients who enrolled into this study. Full Analysis Set (FAS): all patients to whom study treatment has been assigned and who received at least one dose of study treatment. Patients will be analyzed according to the treatment they have been assigned to. Efficacy variables will be analyzed based on the FAS as the primary population. Safety Set (SAF): all patients who received at least one dose of study treatment. Patients will be analyzed according to the study treatment received. The safety population will be used for the analyses of safety variables. Per Protocol Set (PP): all patients in the FAS and have no major protocol deviations. PP population will be used for efficacy analysis. **Demographic and other baseline characteristics** Demographic and other baseline data including laboratory test will be listed and summarized descriptively for all patients in the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented. Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term for all patients as well. **Treatments** The overall duration will be summarized by treatment group using mean, standard deviation, median, minimum and maximum. The number and percentage of patients will be summarized by treatment group for categorized duration group. Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the ATC classification system for the safety population. McNemar Test and Wilcoxon sign rank test will be used to assess the difference in proportions between treatments. Summary tables will be reported to show the changes from baseline to Month 3, and 6 post-indexing and changes from Month 6 to Month 9, and 12 post-indexing date for each variable involved. Normality will be checked for the 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.
Key words	Ventricular arrhythmias; heart failure reduced ejection fraction; implanted device; treatment; healthcare resource utilization

[redacted]

1 Introduction

1.1 Background

Heart failure (HF) is a public health issue around the world including China. In China, the prevalence of HF is estimated approximately 1.3% among Chinese between 35-74 years old. HF imposes a significant economic burden and poor quality of life of patient. Sudden cardiac death is responsible for half of all heart disease deaths. In Europe, the incidence of sudden cardiac death is estimated between 350,000 and 700,000 people annually (Lippert et al 2010). The estimated sudden cardiac death cases in China was 544000 deaths in 1.3 billion people every year (Hua et al 2009).

Angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blockers (ARB) antagonize the action of angiotensin II, a known precursor of interstitial fibrosis that is associated with ventricular arrhythmia (VA). ACEI has been used in patients with HF with reduced ejection fraction (HFrEF) over the past 2 decades. However, despites advances in pharmacological and device therapies, 50% of HF patients die within 4 years and 40% of HF patients admitted to hospital die or are readmitted within a year (ESC Guidelines 2008).

Sacubitril/valsartan is an angiotensin receptor neprilysin inhibitor (ARNI) that providing concomitant neprilysin (neutral endopeptidase 24.11, NEP) inhibition and angiotensin II type 1 (AT_1) receptor blockade. Sacubitril is a neprilysin inhibitor that inhibits the degradation of natriuretic peptides. Valsartan is an angiotensin receptor blocker that mediates the deleterious effects of angiotensin II on the cardiovascular system. Neprilysin is a ubiquitous metallopeptidase with several different substrates that cleaves vasoactive peptides with vasodilation effects (including natriuretic peptides, adrenomedullin, bradykinin, and peptides with vasoconstrictor effects). As a result of neprilysin inhibition, there are an increase of natriuretic peptides in the circulating levels, which then leads to a cardioprotective effect that counteract the detrimental effects of renin-angiotensin system and sympathetic nervous system activation (Huber and Brown 2016).

There are multiple mechanisms that may be implicated in sudden cardiac death in HFrEF patients including VA, asystole, electromechanical dissociation and cardiogenic shock. Sarrias and Bayes-Genis (2018) proposed a mechanism whereby ARNI exerts anti-arrhythmic effects by reducing myocardial cell death, hypertrophy, fibrosis and inflammation through reducing the substrates required for VA. Increase of enkephalins, endorphins, and bradykinin may also play a role in the cardioprotective and anti-arrhythmic effects of neprilysin inhibitors. However, the precise mechanism still remains unknown (Sarrias and Bayes-Genis 2018).

Results of the completed pivotal study, “The prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor with an Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial” found that ARNI was superior compared to ACEI in reducing the risks of death in HFrEF patients and reduce the risk of sudden death (McMurray et al 2014). In PARADIGM-HF trial, there are fewer patients’ experiences serious adverse events (SAE) on ARNI than on ACEI, and fewer patients who received ARNI discontinued study due to adverse events (AE) compared to those patients who received ACEI. Hypotension was more frequently reported in ARNI patients than ACEI patients. Hyperkalemia, cough and renal dysfunction were more commonly reported in ACEI patients than ARNI patients.

[redacted]

Both implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy-defibrillator (CRT-D) are device-based therapies prescribed for HF patients who are diagnosed with arrhythmia or have an increased risk for arrhythmia-related sudden death. The ESC guidelines on cardiac pacing and CRT recommend prophylactic ICD or CRT in HF patients with an ejection fraction ≤35% (ESC Guidelines 2013). In 2013, approximately 2 ICD or CRT-D implantation cases were found among every million people in 2013 in China (National Center for Cardiovascular Diseases 2014). The placement of ICD and ICD-CRT improves survival and reduces sudden death rates in appropriately selected HFrEF patients (Moss et al 2009).

A previous study shown that ARNI significantly decreased sustained ventricular tachycardia (SVT), non-sustained ventricular tachycardia (NSVT), and premature ventricular contraction (PVC) in 120 patients with ICD or CRT-D (de Diego et al 2018). Nevertheless, de Diego et al study had limitation of low sample size and the study was a single-center study. Hence, our study will provide additional value to access the VA prevention role of ACEI/ARB and ARNI for HF patients receiving ICD or CRT-D.

A more recent retrospective study had studied the VA prevalence in relation to ARNI initiation in 151 patients who received ACEI or ARB in a single tertiary HF clinic in Belgium. Significant reductions were observed in ventricular tachycardia/fibrillation (VT/VF), occurrence of appropriate therapy, NSVT, and PVC. Improvement was observed in anti-tachycardia pacing (ATP) in patients with <90% ATP at baseline. The study found out that VA events reduction might be related to left ventricular reverse remodeling (Martens et al 2019). However, this study did not have measurements on N-Terminal prohormone of Brain Natriuretic Peptide (NT-proBNP).

To the best of our knowledge, there is a lack of understanding of the relationship between treatment (ACEI/ARB and ARNI) and VA in HFrEF patients with ICD or CRT-D in China.

1.2 Purpose

The purpose of this study is to generate effectiveness data of ARNI, in the Chinese HFrEF patients with implanted ICD or CRT-D.

2 Objectives and endpoints

This study aims to explore the effect of ARNI on VA and ICD or CRT-D shocks and ATP. The objectives and related endpoints are further described in Table 2-1.

Table 2-1 Objectives and related endpoints

Objectives	Endpoints
Primary Objective • To assess the proportion of patients with VA events over 6 months of ACEI/ARB and 6 months of ARNI treatment	**Endpoint for primary objective** • Proportion of patients with VA events over 6 months of ACEI/ARB and 6 months of ARNI treatment (VA events are defined as SVT, NSVT and PVC, ICD shock and ATP, the definitions of SVT, NSVT, PVC, ATP are as below)

[redacted]

Objectives	Endpoints
Secondary Objectives	**Endpoints for secondary objectives**
• To assess the number of occurrences of VA events and ICD or CRT-D shocks over 6 months of ACEI/ARB and 6 months of ARNI treatment	• Numbers of NSVT, SVT, PVC, ICD shock and ATP experienced by patients 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	• LVEF (%) over 6 months of ACEI/ARB and 6 months of ARNI treatment • NYHA level over 6 months of ACEI/ARB and 6 months of ARNI treatment
• To compare the changes in the NT-proBNP level between ACEI/ARB and ARNI treatments	• NT-proBNP (pg/mL) level over 6 months of ACEI/ARB and 6 months of ARNI treatment
• To compare the healthcare resource utilization of HF patients during ACEI/ARB and ARNI treatments	• Number of hospitalizations for arrhythmia or HF related hospitalizations over 6 months of ACEI/ARB and 6 months of ARNI treatment
[redacted]	

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; [redacted]; ARB = angiotensin receptor blockers; ARNI = angiotensin receptor neprilysin inhibitor; ATP = anti-tachycardia pacing; CRT-D = cardiac resynchronization therapy-defibrillator; HF = heart failure; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; NSVT = non-sustained ventricular tachycardia; NT-proBNP = N-Terminal prohormone of Brain Natriuretic Peptide; NYHA = New York Heart Association; PVC = premature ventricular contraction; SVT = sustained ventricular tachycardia; VA = ventricular arrhythmias

Note:
Sustained ventricular tachycardia is defined as tachycardia with hemodynamic disorder or lasting for ≥30 seconds.
Non-sustained ventricular tachycardia is defined by different ICD devices.
Premature ventricular contraction is defined as an early ventricular depolarization as determined by the device.
Anti-tachycardia pacing is defined as a low-energy alternative to high-energy biphasic shocks

2.1 Primary estimands

The primary clinical question of interest is: What is the effect of the ARNI versus ACEI/ARB on change on VA and ICD or CRT-D shocks and ATP in patients with implanted ICD or CRT-D?

The justification for the primary estimand is that it will capture both the effect of the study drug and the effect of additional medications, mirroring the conditions in clinical practice. Further details can be found in Section 12.

The primary estimand is described by the following attributes:

[redacted]

1. Population: patients defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval. Further details about the population are provided in Section 5.
2. Variable: VA, ICD and ATP events over 6 months of ACEI/ARB and 6 months of ARNI treatment.
3. Treatment of interest: ACEI/ARB for 6 months and ARNI for 6 months. Further details about the investigational treatment and control treatment are provided in Section 6.

Handling of remaining intercurrent events:

1. Treatment discontinuations for any reason: ignore (treatment policy strategy).
2. Unforeseen change in the dose of allowed concomitant medications: ignore (treatment policy strategy).
3. Unforeseen change in the dose of the investigational treatment or the control treatment due to adverse event or other reason: ignore (treatment policy strategy).

The summary measure: Proportion of patients with VA, ICD and ATP events over 6 months of ACEI/ARB and 6 months of ARNI treatment

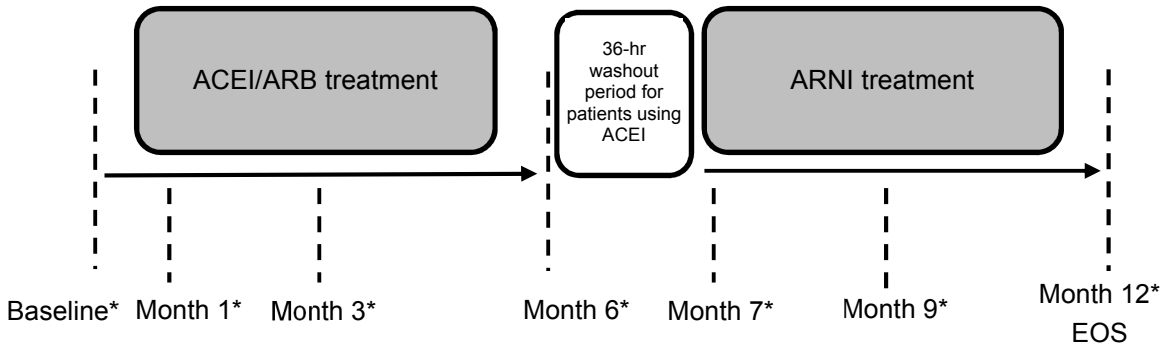
2.2 Secondary estimands

None.

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 (Figure 3-1).

Figure 3-1 Study design



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

Note:

- *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 6-2 and Table 6-3).
- 36-hr washout period is not needed for patients using ARB.

Patients will be informed about the study purpose and asked to sign an informed consent form. Demographics, etiology of HF, comorbidities, New York Heart Association (NYHA) class, baseline laboratory, electrocardiogram, echocardiogram, medical treatment, and implanted device (ICD or CRT-D) type and date will be collected at Baseline. Device data of patients will be collected for 12 months. Once the device is implanted, ACEI/ARB will be given to the patient. 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. The recommended starting dose of ARNI is presented in Table 6-3.

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.

A Central Review Committee which composed by 2 separated subgroups. Subgroup 1 will be formed to confirm the type of events as defined by the device. If there are any discrepancies or disagreements in review, the Chairman will provide a final decision. The events that will be reviewed periodically include: appropriate shocks, inappropriate shocks, SVT, NSVT, PVC, ATP, [redacted]. Subgroup 2 will review SAE reports.

An Academic Committee composed by 11 members of certified electrophysiologists is formed to design and revise this study.

4 Rationale

4.1 Rationale for study design

The purpose of this study is to generate effectiveness data of ARNI, in the Chinese HFrEF patients with implanted ICD or CRT-D.

The rationale of this study is to compare the effect of ACEI/ARB with the effect of ARNI on VA events for HFrEF patients with ICD or CRT-D, thus a multicenter, interventional, open-label, and prospective single-arm study was considered.

4.2 Rationale for dose/regimen and duration of treatment

The dosage of ARNI will be according to investigator's discretion and up titrate to the maximum dosage the patient can tolerate or 200 mg bid. In addition, 6-month is long enough to see the VA events changes after switch to ARNI.

Major clinical trials have established ACEI/ARB treatment as the standard of care for RAAS blockade and ACEI/ARB is recommended by treatment guidelines as the treatment of choice for HFrEF patients. ACEI/ARB has been shown to be superior to placebo in reducing mortality in HFrEF and is mostly used as comparator in large randomized controlled trials in HF.

[redacted]

4.3 Rationale for choice of control drugs (comparator) or combination drugs

ACEI/ARB are chosen as the comparator in this study. The ACEI/ARB treatment has been used as the standard of care for RAAS blockade and is recommended by treatment guidelines as the first-line treatment for HFrEF patients (Yancy et al 2017).

4.4 Rationale for public health emergency mitigation procedures

In the event of a public health emergency as declared by local or regional authorities (i.e., pandemic, epidemic or natural disaster), mitigation procedures may be required to ensure participant safety and trial integrity and are listed in relevant sections of the study protocol. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by local or regional health authorities and ethics committees as appropriate.

4.5 Purpose and timing of interim analyses/design adaptations

The study will have one interim analysis (IA) and one final analysis (FA). The intent of the interim analysis is to stop for futility or high incidence of safety events and re-evaluate minimum sample size required. It is planned once at least 110 patients (half of the required sample size) have completed the study. All study endpoints stated in Section 2 will be analyzed.

4.6 Risks and benefits

Appropriate eligibility criteria and specific dose-limiting toxicity definitions, as well as specific dose modification and stopping rules, are included in this protocol.

The risk to patients in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring.

Women of child-bearing potential must be informed that taking the study treatment may cause injury and death to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements. If there is any question that the patient will not reliably comply, they should not be entered in the study.

The overall benefit-risk balance of ARNI is positive for the treatment of HF (NYHA class II-IV) in patients with systolic dysfunction.

In the context of COVID-19 pandemic, there is still lack of evidence about the risks or benefits of ARNI and ACEI/ARB in COVID-19 patients.

5 Study Population

The study population will consist of approximately 219 patients with HFrEF (left ventricular ejection fraction [LVEF] ≤40%) in 25 sites, aged between 18 years and 80 years, receiving ICD/CRT-D devices.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

[redacted]

1. Male or female patients ≥18 and ≤80 years of age.
2. Implanted with an ICD or CRT-D within 2 weeks.
3. NYHA functional class II – IV.
4. LVEF ≤40% (measured by echocardiography).
5. Signed informed consent must be obtained prior to participation in the study.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes.
2. Patient received target dose (≥200 mg/d) of ARNI for 2 weeks continuously within the 6-week period prior to study enrollment.
3. Participation in other clinical studies 3 months prior to participating study.
4. Advanced cancer or other significant comorbidities with life expectancy of <1 year.
5. Previous history of angioedema associated with ACEI/ARB treatment, hereditary or idiopathic angioedema.
6. Patients with renal artery stenosis history.
7. Current stage D HF patients requiring vasoactive drugs.
8. Symptomatic hypotension < 100/60 mmHg at visit 1 (screening) or Symptomatic hypotension < 90/60 mmHg in anti-hypertension drug treatment at visit 1 (screening).
9. Serum potassium >5.4 mmol/L at visit 1 (screening).
10. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 as measured at visit 1 (screening).
11. Pregnant or nursing (lactating) women.
12. Other exclusion depend on investigator's discretion.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Investigational and control drugs are summarized in Table 6-1 (no limitation to the list).

Patients will receive ACEI/ARB, where generics are acceptable and listed in Table 6-1. Patients will initiate ARNI treatment after a 36-hr washout period after the ACEI treatment. Basically, initiated ARNI dosage accord to ACEI/ARB alternative dosage, but investigators have discretion to prescribe ARNI dosage.

Table 6-1 Investigational and control drug

Drug (Name)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (local)
Investigational Drug				

[redacted]

Drug (Name)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (local)
Sacubitril/Valsartan, 50mg	Tablet	Oral use	Open label subject packs;	supply
Control Drug				
ACEI				
Enalapril	Tablet	Oral use	Open label subject packs;	No supply
Captopril, 6.25 mg, 50 mg	Tablet	Oral use	Open label subject packs;	No supply
Perindopril, 2 mg, 8 mg	Tablet	Oral use	Open label subject packs;	No supply
Ramipril, 1.25 mg, 10 mg	Tablet	Oral use	Open label subject packs;	No supply
Benazepril, 2.5 mg, 20 mg	Tablet	Oral use	Open label subject packs;	No supply
ARB				
Candesartan, 4 mg, 32 mg	Tablet	Oral use	Open label subject packs;	No supply
Valsartan, 40 mg, 160 mg	Capsule	Oral use	Open label subject packs;	No supply
Losartan, 25 mg, 150 mg	Tablet	Oral use	Open label subject packs;	No supply

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Supply of study treatment

ARNI drugs will be supplied in this study by Novartis. Open drug label should be attached on each pack before transport to every site. Every site is responsible for drug storage, drug dispense, drug recycle and recording by documents.

6.1.4 Treatment arms/group

This is a single-arm study.

[redacted]

6.1.5 Treatment duration

The planned duration of treatment for ACEI/ARB and ARNI is 6 months each. During the ACEI/ARB period, the drug choice and dosage are at the discretion of the physician. The EOS will occur when the pre-specified number of patients completed the 12 months treatment. Patients may be discontinued earlier due to unacceptable toxicity and/or treatment is discontinued at the discretion of the investigator or the patient. For patients who in the opinion of the investigator are still deriving clinical benefit from ARNI, every effort will be made to continue provision of study treatment.

6.2 Other treatments

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded on the appropriate electronic Case Report Forms (eCRF).

Each concomitant drug must be individually assessed against all exclusion criteria and prohibited medication. If in doubt, the Investigator should contact the Novartis medical monitor before allowing a new medication to be started. If the patient is already enrolled, contact Novartis to determine if the patient should continue participation in the study.

The concomitant use of other ACEIs or ARBs is strictly prohibited while the patient is receiving ARNI. Study medication should be stopped the day prior to addition of other ACEIs or ARBs.

Drugs for arrhythmia include antiarrhythmic drugs (amiodarone), beta-2 blockers (metoprolol sustained release tablets), and digitalis drugs (digoxin).Except for titration dose adjustment of beta-2 beta blockers, no special dose adjustment for other drugs. Amiodarone dosage must be consistent for patient treatment during this study, if radiofrequency ablation is necessary, the patient should withdraw from the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

The patient should be on an optimal medical regimen of background HF medications. Use of an aldosterone antagonist should be considered in patients eligible for this study. Every effort should be made to keep the dose level of disease-modifying HF medications stable throughout the entire study. However, if the investigator believes a disease-modifying medication is causing an AE or patient's condition needs a change in any of disease-modifying HF medications, it is allowed at the discretion of the investigator. Diuretics may be used and may be adjusted throughout the length of the study at the discretion of investigator.

If patients experience any AEs that may be related to the study drug, other HF medications, or other cardiovascular medications, the investigator should adjust non-disease-modifying medications (e.g. calcium channel blocker, nitrates, α-blockers, and diuretics) first in attempt to alleviate the AEs.

Potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, aldosterone antagonists, and any other medications known to raise potassium levels should be used with caution. The investigator should assess patient's potassium levels, especially in those who are receiving these medications.

[redacted]

Phosphodiesterase-5 inhibitors should be used with caution while the patient is receiving study medications due to the increased possibility of occurrence of hypotension.

In case the patient requires the concomitant administration of neseritide and/or intravenous nitrates with the study medications, the investigator should consider starting them at a lower dose or a slower infusion rate while monitoring the patient's blood pressure carefully.

Nonsteroidal Anti-Inflammatory Drugs

In patients who are elderly, volume-depleted, or with compromised renal function, concomitant use of nonsteroidal anti-inflammatory drugs, including cyclooxygenase-2 (COX-2) inhibitors, with sacubitril/valsartan may result in worsening of renal function, including possible acute renal failure.

Lithium

Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists and ARBs. There is no data on this interaction as for now. Base on related data, serum lithium concentration should be monitored when concomitant sacubitril/valsartan with lithium supplement.

6.2.2 Prohibited medication

Followed by ARNI instructive document. Concomitant use of ARNI with an ACEI/ARB is contraindicated because of the increased risk of angioedema.

Bile acid sequestrants (cholestyramine and colestipol) are also prohibited to avoid disturbing effect on the drug absorption of study medication.

6.2.3 Rescue medication

There is no rescue medication, however in the event of hyperkalemia, investigator should review the medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia. Any patient who experiences a potassium level > 6.0 mmol/L confirmed by repeated same blood sample testing may be discontinued from the study treatment.

If symptomatic hypotension occurs, correct any treatable cause. If hypotension persists, any anti-hypertensive drug and non-disease-modifying drugs, such as diuretics, calcium channel blockers, nitrates, and α-blockers, should be down-titrated or stopped. If hypotension persists, the study drug should be temporarily withdrawn, the re-initiation of ARNI will be at Investigator discretion. ARNI is unlikely to be removed by hemodialysis because of high protein binding.

If ICD electrical storm occurs, correct the underlying arrhythmia. Differential diagnosis to the arrhythmia should be determined, with patient hospitalized and observed by an electrophysiologist. Drugs such as amiodarone and anti-arrhythmic agents can be used.

[redacted]

6.3 Patient numbering, treatment assignment, randomization

6.3.1 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.

6.3.2 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.

6.4 Treatment blinding

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

6.5 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.

6.5.1 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 6-2). The recommended starting dose of ARNI for different population is presented in (Table 6-3). 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 6-2 Recommended dosage

Compound	Initiation dosage	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		

[redacted]

Compound	Initiation dosage	Target dosage
Candesartan	4 mg qd	32 mg qd
Valsartan	40 mg bid	160 mg bid
Losartan	25 – 50 mg qd	150 mg qd

Table 6-3 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

6.5.2 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.

6.5.3 Dose modifications

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

6.5.4 Follow-up for toxicities

Not applicable.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using drug tablet counts and information provided by the patient or guardian via a self-administered diary card. Compliance should be ensured by the investigator to be > 80%. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

[redacted]

6.6.2 Recommended treatment of adverse events

At present there is insufficient information to provide specific recommendations regarding treatment of AEs.

Medication used to treat AEs must be recorded on the appropriate eCRF.

6.6.3 Emergency breaking of assigned treatment code

Not applicable.

6.7 Preparation and dispensation

Each study site will be supplied with ARNI in packaging as described under investigational section. Storage must obey instructional request.

Authorized investigator and drug administrator are responsible for dispensing drug at visit 4, 5, 6 and recycling at visit 5, 6, 7. The number of ARNI distributed was calculated according to the investigator's order and the window period of treatment, and was distributed in the smallest unit, namely box. If titration adjustment is happened between two continuous visits, enough ARNI dose should take into investigator’s consideration to avoid drug shorting, or investigators are responsible for reminding patient to go to site and receipt supplementary ARNI in time.

Patients must take medicine follow by doctor advice, return ARNI pack and the redundant drug. After returning back drugs at visits, authorized investigator and drug administrator are needed to check the drug tablet accord with their diary card and assess patient compliance.

In case the ARNI dosage is not enough for monthly titration modification, the investigator is obligated to remind the patients to return the site and dispense ARNI.

ACEI/ARB is prescribed by the investigators according to the clinical routine.

During the COVID-19 pandemic in which on-site study visits may be impacted, delivery of study treatment directly to a patient’s home is generally permitted. If delivery is not available, patients may purchase the study drugs themselves. Patients will be reimbursed for the study drug cost with drug packaging as proof of purchase.

6.8 Handling of study treatment and additional treatment

6.8.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

6.8.2 Handling of additional treatment

Not applicable.

[redacted]

6.8.3 Instruction for prescribing and taking study treatment

The study drug dosage will be under investigator's discretion according to local guideline and product label (Table 6-2). Patients should take their morning study dose at approximately 08:00 (8 AM) and their evening study dose at approximately 19:00 (7 PM). The study medication should be taken with a glass of water with or without food. If the patient misses taking any study drug dose, he/she should take it as soon as possible, unless if it is almost time for the following scheduled dose. In this case, the patient should skip the missed dose and take the regular study drug administration schedule.

All dosages prescribed and dispensed to the patients and all dose changes during the study must be recorded in the Dosage Administration Record eCRF.

6.9 Treatment of overdose

In the event of an overdose, the Investigator should:

- Contact the medical monitor immediately.
- Evaluate the patient to determine, in consultation with the medical monitor, whether study treatment should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 30 days.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.9.1 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness. For more information on AE and SAE definition and reporting requirements, please see the respective sections.

7 Informed consent procedures

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board/Independent Ethics Committee (IRB/IEC)-approved informed consent.

If applicable, in cases where the patient's representative(s) gives consent (if allowed according to local requirements), the patient must be informed about the study to the extent possible given

[redacted]

his/her understanding. If the patient is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)/ Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the label. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between label updates will be communicated as appropriate, for example, via an investigator notification (IN) or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the patient. In the event of recollection of informed consent is needed, the Investigator may conduct the informed consent discussion remotely (e.g., telephone or video conference). Guidance issued by local regulatory bodies, and ECs/IRBs on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

Women of childbearing potential must be informed that taking the study treatment may involve risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male patients must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Patients who discontinue from the study treatment are to complete the end of treatment visit as soon as possible, and attend the follow-up visits as indicated in Table 8-1.

Patients who discontinue from study should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse events and concomitant medications not previously reported must be recorded on

[redacted]

the eCRF. All treated patients should have a safety follow-up call conducted 30 days after last administration of study treatment.

[redacted]

Table 8-1 Assessment schedule

Period	**Screening**	**ACEI/ARB treatment**			**ARNI treatment**		
Visit name	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Week/Month	0	**1m (± 1w)**	**3m (± 2w)**	**6m (± 2w)**	**7m (± 1w)**	**9m (± 2w)**	**12m (± 2w)**
Obtain informed consent	X						
Inclusion/exclusion criteria	X						
Demography Date of birth Age Gender Race Height (cm) Weight (kg) BMI (kg/m^2) Source of patient referral	X						
Patient HF History	X						
Relevant medical history/current medical history	X						
Prior HF medications	X						
Prior/Concomitant Medications	X	X	X	X	X	X	X
Implanted device Date of implantation ICD or CRT-D Primary prevention or secondary prevention	X						
Device data VA events (SVT, NSVT, PVC) ICD or CRT-D shocks (appropriate shocks and inappropriate shocks) Anti-tachycardia pacing (%)	X	X	X	X		X	X

[redacted]

[redacted]

Physical examinations	X	X	X	X	X	X	X
Electrocardiogram (ECG) data	X		X	X		X	X
Holter monitor	X			X			X
Echocardiographic data LVEF (%) LVEDD (mm)	X			X			X
Vital signs Systolic blood pressure (mmHg) Diastolic blood pressure (mmHg) Heart rate average (bpm)	X	X	X	X	X	X	X
Hematology test Routine blood test Chemistry test Serum potassium (mEq/L) NT-proBNP (pg/mL) eGFR (mL/min/1.73m^2) blood pregnancy test	X			X			X
Urinary pregnancy test	X			X			X
NYHA class (I-IV)	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Hospital admission data	X	X	X	X	X	X	X
Study treatment administration	X	X	X	X	X	X	X
Study treatment dispense (ARNI)				X	X	X	
Diary card collection		X	X	X	X	X	X
Study patient compliance assessment		X	X	X	X	X	X
Study completion status							X

Abbreviations: ACEI = Angiotensin-converting enzyme inhibitor; [redacted]; ARB = Angiotensin receptor blockers;
ARNI = Angiotensin receptor neprilysin inhibitor; [redacted]; CRT-D = cardiac resynchronization therapy-defibrillator;
eGFR = estimated glomerular filtration rate; ICD = Implantable Cardioverter Defibrillators;

[redacted]

LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter;

NSVT = non-sustained ventricular tachycardia; NT-proBNP = N-Terminal prohormone of Brain Natriuretic Peptide;

NYHA = New York Heart Association; PVC = premature ventricular contraction; SVT = sustained ventricular tachycardia

X = assessment to be recorded in the clinical database or received electronically from a vendor; all assessments are requested to do after ICF sign, unless base on discretion from investigators, blood test and imaging report were done within 2 weeks before ICF could be acceptable.

[redacted]

8.1 Screening

All patients must provide informed consent before any study-specific procedure is performed. At Visit 1, patient's eligibility for entering the study will be assessed by the investigator. The date and type of implant with ICD or CRT-D will be recorded. The LVEF measurements required for eligibility will be based on obtained echocardiograms within 2 weeks before this study. Screening NT-proBNP, potassium levels, eGFR and serum creatinine and will be assessed by local hospital lab and only patients with the required values per the entry criteria will be eligible for entering the study.

8.1.1 Information to be collected on screening failures

Patients who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the eCRF. The demographic information, informed consent, and inclusion/exclusion pages must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a serious adverse event during the screening phase (see Section 10.1.3 for reporting details).

Patients who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition eCRF.

8.2 Patient demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with eCRF.

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, gender, race, and source of patient referral. Relevant medical history/current medical history includes data until the start of study drug. Where possible, diagnoses and symptoms will be recorded. HF medications other relevant medical history will be recorded on eCRFs separately.

8.3 Efficacy assessments

8.3.1 Primary efficacy endpoint

Ventricular arrhythmia events

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

[redacted]

3. Premature ventricular contraction is defined as an early ventricular depolarization as determined by the device, and/or detected by Holter

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

Anti-tachycardia pacing and implantable cardioverter-defibrillator shocks

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.

Patients with sustained VA events will receive ICD or CRT-D shock therapy. Inappropriate shocks may occur in patients 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 was redetected by the ICD. If a subsequent episode started within 5 minutes after the previous episode ended, it was not considered as a new episode (van Rees et al 2011).

Proportion of patients had ATP, ICD or CRT-D shocks occurrence over 6 months of ACEI/ARB and 6 months of ARNI treatment will be measured.

8.3.2 Secondary efficacy 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]

8.3.4 Appropriateness of efficacy assessments

The efficacy assessments selected are standard for this indication/participant population.

8.4 Safety assessments

Safety assessments are specified in Table 8-2 with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

Table 8-2 Assessment & specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed at Visit 1, Month 6 and EOS. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include blood pressure and heart rate measurements at every visit. After the patient has been sitting for 5 minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured 3 times using an automated validated device, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 – 2-minute intervals and the mean of the 3 measurements will be used. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Clinically notable vital signs are defined in Appendix 1.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Table 8-1.

8.4.1 Laboratory evaluations

Hematology, chemistry tests, NT-proBNP tests, Pregnancy Test (Table 8-3) will be measured by investigators' hospital lab at baseline, Month 6 and EOS. Clinically significant abnormalities must be recorded as either medical history/current medical conditions or AEs as appropriate.

Clinically notable laboratory findings are defined in Appendix 1.

The eGFR to determine eligibility of the patient for screening will be calculated at Visit 1 from the serum creatinine concentration by using the following formula (Stevens et al 2006):

eGFR (mL/min/1.73 m^2) = 175 x (standardized S_{Cr} in mg/dL)$^{-1.154}$ x (age in years)$^{-0.203}$ x (0.742 if female), where S_{Cr} is the standardized serum creatinine value

The eGFR will also be measured at Month 6 and EOS in order to guide the investigator to take any appropriate action as necessary. Patient will be treatment discontinuation or suspend from the study if eGFR decrease > 50% of baseline value according to investigator decision.

[redacted]

Table 8-3 Laboratory Assessments

Test Category	Test Name
Hematology	Red blood cells count, white blood cells count, platelet count, hemoglobin, hematocrit, and WBC differential
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, lipid profile, hemoglobin A1C
Kidney function	serum creatinine
Biomarkers	NT-proBNP
Pregnancy Test	Serum/Urine pregnancy test

8.4.2 Electrocardiogram (ECG)

Electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position to ensure a stable baseline/according to the ECG investigator manual. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

A 12-lead ECG Holter recording will be performed to capture comprehensive ECG. In addition, 12-lead ECGs are collected at the study site using an ECG machine for safety assessment in real time by a qualified physician to ensure patient safety. Only clinically significant abnormalities must be reported as AE.

In the event that a clinically significant ECG abnormality is identified at the site (e.g., severe arrhythmia, conduction abnormality of QTcF > 500 ms), and the ECG is repeated to confirm the diagnosis. If the patient is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example, cardioversion).

Clinically significant abnormalities must be recorded on the eCRF as either medical history/current medical conditions or AE as appropriate in related visit.

ECG data will be collected at baseline, Month 3, 6, 9 and EOS.

8.4.2.1 Cardiac imaging

LVEF (%) and left ventricular end diastolic diameter (LVEDD) (mm) will be measured by echocardiography at baseline, Month 6 and EOS.

8.4.2.2 Holter

Holter monitoring constantly records heartbeats for 24 hours and can detect arrhythmia events that might be missed by using the ECG. Data of Holter monitoring will be collected at baseline, Month 6 and EOS.

[redacted]

8.4.2.3 Cardiac enzymes

Not applicable.

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

Pregnancy testing is required for pre-menopause women at baseline, visit 4, visit 7 of the trial. At baseline a urinary and a blood pregnancy test should be performed. If positive, the patient should be excluded. If the unpredicted pregnancy happens in the study (visit 4, 7), the patient must be discontinued from study treatment.

8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

8.5 External central review committee

A central review committee is responsible for periodic study endpoint events adjudication and SAE review in Rhythm Study. The central review committee is an independent group consisting of individuals who have experience and expertise in the management of trial participants within heart failure area and in the monitoring of ICD/CRT-D device. The review committee will be separated to two subgroups to perform device data adjudication and SAE review respectively.

Device data report will be exported timely into PDF version by doctors at baseline, 1 month, 3 months, 6 months, 9 months, 12 months when patient visits happen in local sites and all uncertain device events will be sent to the subgroup 1 for adjudication (Device Data adjudication Boards).

All aggregated SAE data will be provided to the subgroup 2 for review (Data and Safety Monitoring Boards, DSMB).

Then committee will have a meeting held by chairman either in the site or by conference call when necessary. Central review committee members will make every attempt to attend the meeting in person or by conference call. Total central review committee members will review and interpret device data (include VA events, ICD-shock, ATP, etc) and aggregated SAE data.

The central review committee members vote on all decisions. The member must be present in the meetings or must have given written recommendation to the chair prior to the meeting. Voting is by voice vote, but any members may request a secret written ballot. After decision making, the Chairman will provide minutes of the Board discussions to all Board members provide a summary (executive) report of each Board meeting to Novartis. A summary statement and recommendation from chairman will be provided in writing to the Novartis Medical Responsible within three working days of each meeting. The recipients will acknowledge receipt and provide a response, if necessary. If an urgent report (defines according to investigator discretion) is needed to interpret, at least 3 committee members should response and give their consensus decision to the investigator.

Committee Responsibility:

1. Endpoints adjudication use for final study

[redacted]

2. Provide clinical suggestion to investigators
3. Make amendment for protocol to NVS, for example patient exclusion and enrollment criteria.

8.6 Additional assessments

No additional tests will be performed on participants entered into this study.

8.6.1 Clinical outcome assessments

Not applicable.

8.6.1.1 Additional biomarker assessments

Not applicable.

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment for a patient occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the investigator.

The investigator must discontinue study treatment for a given patient if, he/she believes that continuation would negatively impact the patient's well-being.

Discontinuation from study treatment is required under the following circumstances:

1. Patient/guardian decision
2. Pregnancy
3. Use of prohibited treatment as per recommendations in the prohibited treatment section
4. ACEI/ARBs daily dosage below guided dosage last for 1 month
5. Any situation in which study participation might result in a safety risk to the patient
6. Withdrawal of informed consent

Study treatment may be discontinued at the investigator's discretion if any of the following occurs:

1. Any severe, or suspected AE, that may jeopardize patient well-being, if the study drug is continued
2. Suspected occurrence of angioedema
3. Serum potassium >6.0 mmol/L at follow Visit
4. Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study

If discontinuation of study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the patient's premature discontinuation of study treatment and record this information.

[redacted]

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section). **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact the patient/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule. Patients are to be discontinued from the study treatment if patient has not received the study treatment for > 14 days.

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New/concomitant treatments
- Adverse events/SAE

9.2 Withdrawal of informed consent and exercise of participant's data privacy rights

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent (WoC) occurs only when a patient:

- Explicitly requests to stop use of their data,

and

- No longer wishes to receive study treatment,

and

- Does not want any further visits or assessments (including further study-related contacts)

Withdrawal of consent impacts ability to further contact the patient, collect follow-up data (e.g. to respond to data queries) and potentially other restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the Investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the patient has withdrawn his/her consent for the use of data in addition to a study discontinuation.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

If the patient agrees, a final evaluation at the time of the patient's withdrawal of consent/exercise data privacy rights should be made as detailed in the assessment table.

[redacted]

Further details on withdrawal of consent or the exercise of patients' data privacy rights are included in the corresponding informed consent form.

9.2.1 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participants' data privacy rights), the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.2.2 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination (but not limited to):

- Unexpected, significant, or unacceptable safety risk to patients enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study treatment development

In taking the decision to terminate, Novartis will always consider patient welfare and safety. Should early termination be necessary, patients must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The study is only conducted in China, the Investigator or Novartis depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.3 Study completion and post-study treatment

Study completion is defined as when the last patient finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision (e.g. Each patient will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them).

All treated patients should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the patient should be recorded in the source documentation.

Continuing care should be provided by the investigator and/or referring physician based on patient availability for follow-up. This care may include:

- Enrollment in an extension study, if any

[redacted]

10 Safety monitoring and reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 10.1.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.1.3.

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An 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.

The investigator has the responsibility for managing the safety of individual participant and identifying AEs.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of AEs must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade:
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. Its relationship to the study treatment. 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.’ The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single patient.
3. Its duration (start and end dates or ongoing) and the outcome must be reported.

[redacted]

4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met.
5. Action taken regarding with study treatment.

   All AEs must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose reduced/increased
   - Drug interrupted/permanently discontinued
6. Its outcome

Conditions that were already present at the time of informed consent should be recorded in medical history of the patient.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an AE is detected, it must be followed until its resolution or until it is judged to be not recovered/not resolved (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the product label.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

10.1.2 Serious adverse events

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 was 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 were more severe (please refer to the ICH-E2D Guidelines).

[redacted]

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/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 events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

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.

10.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to local Novartis Patients Safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Screen failures

A screen failure occurs when a patient who is screened but is not treated or randomized. SAEs occurring after the patient has provided informed consent until the time the patient is deemed a screen failure must be reported to Novartis.

Treated patients

SAEs collected between time patient signs ICF until 30 days after the patient has discontinued or stopped study treatment.

[redacted]

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an IN to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

If a SAE is unexpected, i.e., the event an adverse reaction, the nature or severity of which is not consistent with the applicable product information and is suspected to be related to the Novartis study drug, this event is considered a Suspected Unexpected Serious Adverse Reaction (SUSAR). SUSARs will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in China.

Any SAEs experienced after the 30-day period after the last study visit should only be reported to the local Novartis Patient Safety if the Investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

In case a female patient becomes pregnant, or plans to become pregnant, the study drug must be discontinued (or, from the date the pregnancy becomes known) for the entire duration of the pregnancy and lactation period (or, for the entire duration that contraception is discontinued). To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Patient Safety. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

10.1.5 Reporting of study treatment errors including misuse/abuse/overdose

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition) (Table 10-1).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

[redacted]

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Overdose is any dose and / or regimen which are over the protocol specified dose/regimen.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE
Overdose	Yes	Yes	Only if associated with an SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.1.6 Reporting of Non-serious Adverse Drug Reactions

An **adverse drug reaction** (ADR) is a response to a medicinal product which is noxious and unintended. An ADR implies at least a reasonable possibility of a causal relationship between a medicinal product and an adverse event.

Non-serious ADRs that occurred in patients exposed to the Novartis drug(s) of interest must also be recorded in the local Novartis Patient Safety database for local regulatory reporting.

The Novartis drug(s) of interest evaluated in this study is/are: Sacubitril/Valsartan

The treating physician or other involved HCP must assess the relationship to the Novartis drug, complete the AE Report Form and send the completed, signed form by fax/ email **within 10 calendar days** to the local Patient Safety department.

The email address, telephone and telefax number of the contact persons in the local Patient Safety department, specific to the site, are listed in the treating physician/HCP folder provided to each site. The original copy of the AE Report Form and the fax confirmation sheet or email must be kept with the CRF documentation at the study site.

10.2 Additional safety monitoring

An external central review committee for this study will also periodically review aggregated SAE data, and make recommendation to sponsor if needed, e.g., protocol amendment on inclusion/exclusion criteria. See Section 8.5 in the protocol for details of the external central review committee.

[redacted]

11 Data collection and database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the Electronic Data Capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated contract research organization [CRO]) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel and/or Novartis designated CRO representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by Novartis personnel and/or Novartis designated CRO. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

[redacted]

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Enrolled Set comprises all patients who enrolled into this study.

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned and who received at least one dose of study treatment. Patients will be analyzed according to the treatment they have been assigned to. Efficacy variables will be analyzed based on the FAS as the primary population.

The Safety Set (SAF) includes all patients who received at least one dose of study treatment. Patients will be analyzed according to the study treatment received. The safety population will be used for the analyses of safety variables.

The Per Protocol Set (PP) includes all patients in the FAS and have no major protocol deviations. PP population will be used for efficacy analysis.

12.2 Patient demographics and other baseline characteristics

Demographic and other baseline data including laboratory test will be listed and summarized descriptively for all patients in the FAS, SAF and PP in separate. Baseline data is defined as data collected during screening phase.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term for all patients as well.

[redacted]

12.3 Treatments

Description on how the exposure data for investigational and other treatment medication will be collected by the assessments have been given in Section 6.3. The treatment duration of this study is 12 months (6 months for each treatment) in total. The overall duration will be summarized by treatment group using mean, standard deviation, median, minimum and maximum. The number and percentage of patients will be summarized by treatment group for categorized duration group.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the ATC classification system for the safety population.

12.4 Analysis of the primary endpoint

The purpose of primary objectives are to explore the effect of ARNI and ACEI/ARB in HFrEF patients with ICD or CRT-D in terms of VA events and in terms of ICD shocks and ATP using primary estimand described in Section 2.1.

In this study, patients will be observed for 6 months under ACEI/ARB alone. Then, ARNI treatment will be initiated (ACEI/ARB stopped, 36-hr washout period applied for patients using ACEI only) and patients will be observed for another 6 months under ARNI.

Multiple primary endpoints will be evaluated in this study during 2 different treatment periods, that are 6 months of ACEI/ARB treatment and 6 months of ARNI treatment (see detailed definitions in Section 12.4.1.)

Since the endpoints are all paired qualitative variable, McNemar Test will be used respectively to assess the difference in primary endpoint proportion between treatments.

12.4.1 Definition of primary endpoint

The endpoints of primary objective are as follow:

1. To explore the effect of ARNI in VA events, ICD shocks and ATP.
    1. Paired proportion of patients by the occurrence of at least one SVT over 6 months of ACEI/ARB and 6 months of ARNI treatment
    2. Paired proportion of patients by the occurrence of at least one NSVT over 6 months of ACEI/ARB and 6 months of ARNI treatment
    3. Paired proportion of patients by the occurrence of at least one PVC over 6 months of ACEI/ARB and 6 months of ARNI treatment
    4. Paired proportion of patients by the occurrence of at least one ICD shocks over 6 months of ACEI/ARB and 6 months of ARNI treatment
    5. Paired proportion of patients by the occurrence of at least one ATP over 6 months of ACEI/ARB and 6 months of ARNI treatment

The VA event, ICD shocks and ATP assessment will be captured by ICD or CRT-D implanted into the patients.

[redacted]

12.4.2 Statistical model, hypothesis, and method of analysis

For all primary endpoints, summaries at baseline, Month 3, 6, 9 and 12 post-indexing date will be reported together. Different hypothesis testing will be done on different types of variables as follow:

Analysis of paired patient proportions

Occurrence events to be considered SVT, NSVT, PVC, ICD 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 x 2 contingency table as follow:

Table 12-1 Matched pairs 2 x 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 is 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 ($b + c < 25$).

12.4.3 Handling of remaining intercurrent events of primary estimand

The analysis will account for different intercurrent events as explained in Section 2.1.

12.4.4 Handling of missing values not related to intercurrent event

No assumptions on the type of missing data will be made (missing completely at random etc.). The comparison using McNemar Test required the proportion observed to be in pair, hence the analysis will be done on complete-case basis.

12.4.5 Sensitivity analyses for primary endpoint/estimand

None.

12.4.6 Supplementary analysis

None.

[redacted]

12.4.7 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 12-1, the maximum likelihood estimate of relative risk (Mantel and Haenszel 1959), $\hat{R}$ is given as follow:

$$\hat{R} = \frac{b}{c}.$$

Null hypothesis: $\hat{R} = 1$ versus alternative hypothesis: $\hat{R} \neq 1$. 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.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy endpoints

Please refer to Section 2 for the secondary objectives. The corresponding secondary variables are listed below:

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

12.5.2 Statistical model, hypothesis, and method of analysis

All the following analysis will be performed on the FAS and PP.

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 shocks experienced, number of ATP experienced and time duration of NSVT experienced.

For each variable, a summary table will be reported to show the changes from baseline to Month 3, and 6 post-indexing and changes from Month 6 to Month 9, and 12 post-indexing date. The changes will be summarized by mean, standard error, median, quartiles, minimum and maximum.

[redacted]

The change from date of treatment in interested endpoint after 6 months of each treatment is calculated by taking the difference between value recorded at the date of first treatment intake and at the date of last treatment intake.

Normality will be checked for the 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.

For each variable, a summary table will be reported to show the changes from baseline to Month 3, and 6 post-indexing and changes from Month 6 to Month 9, and 12 post-indexing date. The changes will be summarized by mean, standard error, median, quartiles, minimum and maximum.

The change from date of treatment in interested endpoint after 6 months of each treatment is calculated by taking the difference between value recorded at the date of first treatment intake and at the date of last treatment intake.

Normality will be checked for the 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.

Other than that, the variables involved before and after the initiation of ARNI will also be analyzed using the same statistical method.

Note that NYHA is a qualitative variable, appropriate data transformation (to be described in Statistical Analysis Plan) will be used to convert it into quantitative form.

12.5.3 Safety endpoints

For all safety analyses, the SAF will be used and there will be no formal statistical inference analysis. All listings and tables will be presented by treatment group.

Safety summaries (tables and figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

Adverse events

All information obtained on AE will be displayed by treatment group and patient.

The number (and percentage) of patients with treatment-emergent AE (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized by treatment, primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related AE, death, SAE, other significant AE leading to discontinuation and AE leading to dose adjustment.

[redacted]

The number and proportion of patients with AE as described in Section 10.1 will be summarized by treatment.

A patient with multiple AE within a primary system organ class is only counted once toward the total of the primary system organ class.

Adverse events which will be counted for a specific treatment period are those which are treatment-emergent. These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of study drug relationship, or developed into SAEs after the start of the treatment period.

Vital signs

All vital signs data (see Section 8.4.2) will be listed by treatment group, patient, 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.

Clinical laboratory evaluations

All laboratory data (see Section 8.4.1) will be listed by treatment group, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Shift tables will be used to compare baseline to the worst on-treatment value.

[redacted]

[redacted]

[redacted]

[redacted]

12.7 Interim analyses

An interim analysis will be conducted once half of the enrolled patients have completed the study.

12.8 Sample size calculation

12.8.1 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:

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

and after substituting P_t and P_s 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).

12.8.2 Power for analysis of selected secondary variables

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

[redacted]

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.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov, In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results.

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality control and quality assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures (SOPs) as well as applicable global/local GCP regulations and ICH Guidelines.

[redacted]

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for patient safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

[redacted]

15 References

References are available upon request

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[redacted]

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

Clinically notable laboratory abnormalities for selected tests based on a percent change from baseline:

Hematology

Red blood cell (RBC) count, hemoglobin and hematocrit: >50% increase, >20% decrease

White blood cell (WBC) count: >50% increase, >50% decrease

Platelet: >75% increase, >50% decrease

Blood chemistry

Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST): >150% increase

Blood Urea Nitrogen (BUN), creatinine and uric acid: >50% increase

Total bilirubin and alkaline phosphatase: >100% increase

Creatinine phosphokinase (CPK): >300% increase

Potassium: >20% increase, >20% decrease

Chloride and calcium: >10% increase, >10% decrease

[redacted]