NOVARTIS

Global Clinical Development - General Medicine

LCZ696B

Clinical Trial Protocol CLCZ696B3302 / NCT04023227

A multicenter, prospective, randomized, open-label, blinded-endpoint, Phase 4 study to evaluate the efficacy and safety of sacubitril/valsartan compared with enalapril on morbidity, mortality, and NT-proBNP change in patients with chronic Chagas' cardiomyopathy

Document type:	Amended Protocol Version
EUDRACT number:	Not applicable
Version number:	03 (Clean)
Clinical Trial Phase:	4
Release date:	10-Nov-2021

Clinical Study Protocol Template Version 2.0 (01-Aug-2018)

Table of contents

List of tables

List of figures

List of abbreviations

ACEIs	angiotensin-converting enzyme inhibitors
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARBs	angiotensin receptor blockers
ARO	academic research organization
AST	aspartate aminotransferase
BID	twice a day
CCC	chronic Chagas' cardiomyopathy
CI	confidence interval
CLIA	chemiluminescent immunoassay
CRT	cardiac resynchronization therapy
CT	computerized tomography
CV	cardiovascular
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report forms
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
ER	emergency room
FAS	full analysis set
GCP	good clinical practice
GGT	gamma-glutamyl transferase
HF	heart failure
HFrEF	heart failure with reduced ejection fraction IB
ICD	implantable cardioverter defibrillator
ICH	international conference on harmonization
IEC	independent ethics committee
IFI	indirect immunofluorescence
IHA	indirect hemagglutination
IN	investigator notification
INR	international normalized ratio
IRB	institutional review board
IWRS	interactive web response system
LVEF	left ventricular ejection fraction
MUGA	multiple gated acquisition scan
MRI	magnetic resonance imaging
NEP	neprilysin
NSVT	non-sustained ventricular tachycardia
NT-proBNP	n-terminal prohormone of brain natriuretic peptide NYHA
PPS	per-protocol set
PVC	premature ventricular contractions
PT	prothrombin time
RAAS	renin-angiotensin-aldosterone system
SAE	serious adverse event

SUSAR	suspected unexpected serious adverse reaction TBL
VT	ventricular tachycardia
WB	western blot

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), saliva, tissue, urine, stool, etc. taken from a study participant
Control drug	A study drug (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 participant in a time unit (e.g., 2.5 mg, twice a day [BID])
Electronic data capture	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive web response systems (IWRS) 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 study	The end of the clinical study is defined as the last visit of the last participant or at a later point in time as defined by the protocol.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Investigational drug/treatment	The drug whose properties are being tested in the study
Low dosage of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)	Less than 50% of the target dosage of background ACEIs or ARBs, i.e., enalapril 2.5 mg BID as opposed to 5 mg BID. These participants should start the study at the minimum dosages of study drugs (enalapril 2.5 mg BID or sacubitril/valsartan 50 mg BID)
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Naïve patients	Patients who are not receiving lifesaving drugs (e.g., newly diagnosis)
Other treatment	Treatment that may be needed/allowed during the conduct of the study (concomitant or rescue therapy)
Patient	An individual with the condition of interest for the study
Period	The subdivisions of the study design (e.g., Follow up) which are described in the protocol. Periods define the study phases and will be used in clinical study database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is transferred to the Academic Research Organization (ARO)/Novartis for the purpose of the clinical study. This data includes participant identifier information, study information, and biological samples
Premature participant withdrawal	Point/time when the participant 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 participant

Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
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
Standard dosage of ACEIs/ARBs	At least 50% of medium or standard ACEI/ARB dosage, i.e., enalapril 5 mg BID or higher, or valsartan 80 mg BID or higher. These participants should start study drug at medium dosages of study drugs (enalapril 5 mg BID or sacubitril/valsartan 100 mg BID)
Start of the clinical study	The start of the clinical study is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the participant as part of the required study procedures
Study treatment discontinuation	When the participant permanently stops taking any of the study drugs 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
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Treatment arm	A treatment arm defines the dose and regimen or the combination, and may consist of 1 or more cohorts
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent samples "	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data.

Amendment 3 (10-Nov-2021)

Amendment rationale

This amendment was implemented to clarify some eligibility criteria, add COVID-19 related exclusion criteria, clarify remote procedures, clarify dose titration for subjects previously receiving higher dosages of ACEi or ARBs and allocated to the enalapril arm, clarify rationale for discussion of mitigation actions in case of public health emergencies and include additional clarifications as detailed below.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version as following:

- Sec. 3: Clarifications about remote procedures.
- Sec. 3.2.1: Clarification regarding dose titration for subjects receiving higher dosages of ACEi or ARBs prior to randomization and allocated to the enalapril arm.
- Sec. 4.6: Section added in order to clarify the rationale for implementation of public health emergencies mitigation actions
- Sec. 5.1: Inclusion criteria #4 was edited in order to clarify Chagas' serology accepted tests.
- Sec. 5.2: Exclusion criteria edited in order to add COVID-19 related criteria, add clarification about past use of sacubitril/valsartan and clarify exclusion criterion related to gastrointestinal form of chronic Chagas' disease.
- Sec. 8: note added to table of events.
- Sec. 8.5.1: In the biomarkers section, added that *T. cruzi* serology in addition to parasitemia will be performed.(no additional sample required)
- Sec. 9.1.1: Clarification added to discontinuation of study treatment section.

Institutional Review Boards/Independent Ethics Committees

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

The changes described in this amended protocol require IRBs/IECs and/or HAs approval according to local regulations prior to implementation.

The model informed consent form will be updated to include the optional consent for activities that may be done outside of the study site.

Summary of previous amendments

Amendment 2 (11-Aug-2020)

Amendment rationale

This amendment was implemented to include additional assessments in a subset of participants: biomarkers (approximately 550 patients), Holter monitoring (400 patients), and magnetic resonance imaging (MRI) (100 patients), with the purpose to gain deeper insight into the clinical and molecular mechanisms of CCC and the impact of the study treatments.

The study started on 10-Dec-2019, approximately 12 participants have been recruited to date. The changes proposed by this amendment will not influence the study population. The knowledge obtained from the study results will be enhanced by including the outcomes of the additional assessments.

Information related to re-screening was also included.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version using strike through red font for deletions and red underlined for insertions.

- Section 8: The additional assessments were added to Table 8-1
- Section 8.1.1: Clarification on re-screening was added
- Section 8.5 "Additional assessments" was added to include the description of the biomarkers, Holter monitoring and MRI analyses
- Section 9.1.2: Clarification added that participants may withdraw consent from the additional assessments and still participate in the Main Study
- Section 12.6: The analysis of biomarkers was added
- Section 15: New references added to support the additional assessments
- Section 16: New sub-sections 16.6 (Holter monitoring) and 16.7 (MRI) were added to the appendices to provide detailed description of these additional assessments

Institutional Review Boards/Independent Ethics Committees

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

The changes described in this amended protocol require IRBs/IECs and Health Authority approval according to local regulations prior to implementation.

The model informed consent form will be updated to include the additional assessments. A separate genetics informed consent form will be created. The study sites are required to submit both informed consent forms for approval.

Amendment 1 (local amendment specific for Colombia)

Amendment rationale

This amendment was implemented to allow the use of 2 tablets of enalapril 5 mg in place of a single tablet of enalapril 10 mg in participating countries, e.g. Where the 10 mg enalapril formulation used in the study is not available commercially.

The study has not yet enrolled its first participant. This change is to allow the administration of the target enalapril dose of 10 mg and has no impact on the study population or study results.

Changes to the protocol

Clarification on how the enalapril 5 mg and 10 mg BID dose level can be covered was added into the following sections:

- Section 6.1.1: Investigational and control drugs
- Section 6.7.2: Instruction for prescribing and taking study treatment

Institutional Review Boards/Independent Ethics Committees

A copy of this amended protocol will be sent to the IRBs/IECs and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein do NOT affect the study-specific model informed consent form.

Protocol summary

Protocol number	CLCZ696B3302
Full Title	A multicenter, prospective, randomized, open-label, blinded-endpoint, Phase 4 study to evaluate the efficacy and safety of sacubitril/valsartan compared with enalapril on morbidity, mortality, and NT-proBNP change in patients with chronic Chagas' cardiomyopathy
Brief title	Study of the efficacy and safety of sacubitril/valsartan compared to enalapril on morbidity, mortality, and NT-proBNP change in patients with CCC
Sponsor and Clinical Phase	Novartis, Phase 4
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the effect of sacubitril/valsartan 200 mg BID compared with enalapril 10 mg BID, in addition to conventional heart failure (HF) treatment, in improving a hierarchical composite of cardiovascular (CV) events (i.e. CV death or the occurrence of first HF hospitalization) and causing a greater reduction in n terminal prohormone of brain natriuretic peptide (NT-proBNP, at Week 12 from Baseline) in participants with HF with reduced ejection fraction (HFrEF) caused by CCC. Although there are no prospective studies testing the effects of standard treatment in participants with CCC, the guidelines recommend treating these participants with the same medications indicated for HF due to other etiologies. Our hypothesis is that sacubitril/valsartan is superior to enalapril in reducing a composite of CV events (CV death or first HF hospitalization), or in causing greater reduction or lesser increase in NT-proBNP levels at Week 12 in participants with HFrEF caused by CCC.
Primary Objective(s)	To assess whether sacubitril/valsartan is superior to enalapril in improving a composite hierarchical outcome consisting of: a) time to CV death, b) time to first HF hospitalization and c) relative change in NT-proBNP levels between Baseline and Week 12 in participants with HFrEF caused by CCC.
Secondary Objectives	1. To test whether sacubitril/valsartan is superior to enalapril in delaying the time from randomization to first occurrence of hospitalization due to HF or CV death 2. To test whether sacubitril/valsartan is superior to enalapril in delaying the time to death from any cause (all-cause mortality) 3. To test whether sacubitril/valsartan is superior to enalapril in delaying the time to the first occurrence of resuscitated sudden cardiac arrest or sudden cardiac death 4. To test whether sacubitril/valsartan is superior to enalapril in reducing the number of visits to an emergency room (ER) for HF (where intravenous therapy is required) 5. To test whether sacubitril/valsartan is superior to enalapril in increasing the number of days alive out of the hospital
Study design	This is a Phase 4, multinational, multicenter, parallel-group, prospective, randomized, open-label, blinded-endpoint adjudication, active-controlled study to demonstrate superiority of sacubitril/valsartan over enalapril in improving a composite of CV events (CV death or first HF hospitalization), or in causing greater reduction or lesser increase in NT-proBNP levels at Week 12 in participants with HFrEF caused by CCC.
Population	The study participants will consist of men and women with HFrEF (New York Heart Association [NYHA] Class II-IV), aged 18 years or older, with left ventricular ejection fraction (LVEF) ≤ 40% caused by Chagas' disease. The target projected sample size is approximately 900 participants (450 in each arm). It is estimated that approximately 1800 participants will be screened at up to approximately 100 study sites.

Key Inclusion criteria	Written informed consent must be obtained before any study assessment is performed Male or female ≥ 18 years of age Diagnosis of NYHA Class II-IV HFrEF established by: a. LVEF ≤ 40% within 12 months prior to Visit 1 made by any local measurement using echocardiography, multiple gated acquisition scan (MUGA), computerized tomography (CT) scanning, MRI, or ventricular angiography, provided no subsequent measurement above 40% AND b. NT-proBNP ≥ 600 pg/mL (or BNP ≥ 150 pg/mL) at Visit 1 OR c. NT-proBNP ≥ 400 pg/mL (or BNP ≥ 100 pg/mL) at Visit 1 and a hospitalization for HF within the last 12 months Chagas' disease diagnosis confirmed by at least two different serological tests for anti-*Trypanosoma cruzi* based on different principles or with different antigenic preparations, such as: enzyme-linked immunosorbent assay [ELISA], indirect immunofluorescence [IFI], indirect hemagglutination [IHA], western blot (WB), chemiluminescent immunoassay (CLIA). If documented history is not available, the tests may be performed during the screening
Key Exclusion criteria (full list in Section 5.2)	Patients with history of suspected or proven angioedema or unable to tolerate ACEIs,ARBs or ARNI (e.g., due to cough, hypotension, renal dysfunction, hyperkalemia) Use of sacubitril/valsartan in the last 3 months Patients requiring continuous intravenous inotropic therapy or with indication of advanced support intervention for HF: a. already on list for a heart transplantation b. with current indication of left ventricular assist device, or cardiac resynchronization therapy (CRT), Systemic systolic blood pressure lower than 95 mmHg or symptomatic hypotension at Screening (Visit 1) Serum potassium > 5.2 mmol/L at Screening (Visit 1) estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 of body surface area at Screening (Visit 1) Severe gastrointestinal form of chronic Chagas' disease: (demonstrated megaesophagus and/or important megacolon, e.g.: with compromised oral intake or surgical indication). Current confirmed COVID19 infection COVID19 infection with persistent symptom burden suspected due to COVID19
Study treatment	sacubitril/valsartan or enalapril
Efficacy assessments	1. Time from randomization to CV death, or time from randomization to the first HF hospitalization, or relative change from Baseline to Week 12 in NT-proBNP 2. Time from randomization to the first occurrence of a composite of CV events. 3. Time from randomization to all-cause mortality 4. Time from randomization to sudden death or resuscitated sudden cardiac arrest 5. Number of visits to an ER due to HF (where intravenous therapy is required) 6. Number of days alive out of the hospital 7. Number of ventricular fibrillation or sustained ventricular tachycardia needing specific pharmacological, electrical, or other treatment 8. Number of anti-tachycardia pacing or shock therapies

Key safety assessments	• physical examination • vital signs • laboratory evaluations (hematology, clinical chemistry, urinalysis) • pregnancy assessment • electrocardiogram (ECG) • adverse events (AEs) • serious adverse events (SAEs) • adverse events of special interest (angioedema, arrhythmias, symptomatic hypotension, hyperkalemia, and renal dysfunction)
Other assessments	The following additional assessments will be performed in a subset of participants: • Biomarkers • Holter monitoring • Magnetic resonance imaging
Data analysis	The primary endpoint is the hierarchically ordered composite consisting of time to CV death (worst category; earlier time to CV death is unfavorable), time to first HF hospitalization (second worst category; earlier time to HF hospitalization is unfavorable), and the relative change from Baseline to Week 12 in NT-proBNP levels (best category; more reduction or less increase are favorable). CV events will be confirmed by an independent blinded Endpoint Adjudication Committee. The primary efficacy endpoint will be analyzed using the win ratio approach comparing every participant in the sacubitril/valsartan arm to every participant in the enalapril arm to determine a winner. The estimated win ratio (the total number of winners in the sacubitril/valsartan arm divided by the total number of winners in the enalapril arm) and the corresponding 2-sided 95% confidence interval (CI) will be provided. Based on simulations, assuming an annualized rate of 0.20 for the composite of CV death or HF hospitalization in the enalapril group and a 20% hazard reduction in the sacubitril/valsartan group, and assuming a 25% lower geometric mean of NT-proBNP (in terms of ratio of Week 12/Baseline) in the sacubitril/valsartan group, with uniform recruitment over 18 month and a total study duration of 36 months, a study with 900 randomized participants will have 85% power at a one-sided alpha of 2.5%. The study is planned to continue until 302 participants have experienced a CV event and all randomized participants have a minimum follow up of 12 weeks.
Key words	Chagas' disease, heart failure, angiotensin receptor-neprilysin inhibitor, ARB, ACEI

1 Introduction

1.1 Background

Chagas' disease, also called American trypanosomiasis, remains a serious health problem, affecting about 6 million people, mainly in Latin America (WHO 2015). It is also spreading around the world, mostly due to the migration of infected patients to more developed regions, mainly North America and Europe. In these non-endemic areas, there are now almost 400 000 infected people who could potentially transmit the disease through blood transfusion, organ donation, or pregnancy (Nunes et al 2018).

Chronic Chagas' cardiomyopathy (CCC) is considered the most common and serious manifestation of chronic Chagas' disease, occurring in 20 to 30% of infected people (Rassi et al 2010), and it is characterized by chronic myocarditis that involves all cardiac chambers and damage to the conduction system (Nunes et al 2013).

In some endemic areas, CCC may be responsible for 41% of the cases of HF (Bocchi 2013). Moreover, HF caused by Chagas disease is associated with higher mortality compared with HF from other etiologies (Freitas et al 2005, Bocchi 1994). Confirming earlier findings, the estimated mortality rates for CCC at 1, 2, and 3 years was approximately 30%, 44%, and 56%, whereas for non-chagasic etiologies the rates were 12%, 26%, and 39% (Ayub-Ferreira et al 2013). A study among Latin Americans immigrants with non-ischemic cardiomyopathy living in California also showed that CCC was associated with increased all-cause mortality/heart transplantation and HF hospitalization than patients without CCC (despite similar left ventricular end diastolic diameter and LVEF) (Traina et al 2015).

A recently published analysis that included data from the two largest and most contemporaneous HFrEF studies (PARADIGM-HF and ATMOSPHERE) have shown in a subgroup of approximately 200 patients that those with CCC were younger and had lower prevalence of hypertension and diabetes compared with other non-ischemic and ischemic forms of cardiomyopathy (Shen et al 2017). In the same analysis, patients with CCC reported significantly worse health-related quality of life when evaluated with the Kansas City cardiomyopathy questionnaire, while the adjusted risk of CV death was approximately 40% greater compared with ischemic HFrEF patients, despite similar use of contemporaneous treatments.

Hence, the aggressive presentation of the CCC as compared to dilated cardiomyopathies of other origins, has been related to multiple factors such as the persistence of myocardial damage due to immunologic mechanisms directly or indirectly associated with the parasite presence; abnormalities in myocardial perfusion due to microvascular derangements; high rate of ventricular arrhythmias; neurogenic disturbances or Chagas dysautonomy; differences in the neuro-humoral activation, etc. (Nunes et al 2018).

Although there are no studies testing the effects of standard treatment in patients with CCC, the guidelines recommend treating these patients with the same medications indicated for other etiologies (Andrade et al 2011, Bocchi et al 2012).

Interestingly, in the post-hoc analysis of the SHIFT study, Bocchi et al (2018) reported an effect of the I(f) channel inhibitor ivabradine in reducing heart rate and improving functional class in 38 patients with CCC.

Angiotensin-converting enzyme inhibitors have largely been used in the treatment of patients with CCC. Beneficial effects of the ACEI enalapril on left ventricular diastolic function have been reported (Szajnbock et al 1993). High doses of enalapril increase LVEF, improve quality of life, and decrease serum BNP and chemokine concentrations. In patients with CCC, optimization of treatment with enalapril and the mineralocorticoid receptor antagonist spironolactone, and subsequent addition of carvedilol, were safe and associated with benefits in cardiac function and clinical status (Botoni et al 2007).

Sacubitril/valsartan (Entresto®, LCZ696) consists of the neprilysin (NEP) inhibitor sacubitril (AHU377) and the ARB valsartan. Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides, including NPs, bradykinin, and adrenomedullin. Neprilysin inhibition increases the concentrations of these substances, countering the neurohormonal over activation that contributes to vasoconstriction, sodium retention, and maladaptive remodeling.

In the PARADIGM-HF study, sacubitril/valsartan significantly reduced the time to death from CV causes or hospitalization subsequent to HF compared with enalapril after a median follow up of 27 months (McMurray et al 2014), which was the primary endpoint met by 914 participants (21.8%) in the sacubitril/valsartan arm and 1117 participants (26.5%) in the enalapril arm. In addition, sacubitril/valsartan reduced the risk of CV mortality alone by 16% and hospitalization because of HF by 21% compared with enalapril. This study provided evidence to support the replacement of ACEIs or ARBs with sacubitril/valsartan in the management of HFrEF (McMurray et al 2015).

An exploratory post-hoc analysis of the effect of sacubitril/valsartan in a subpopulation of 113 CCC patients in PARADIGM-HF (58 in the sacubitril/valsartan arm and 55 in the enalapril arm) showed that patients with CCC treated with sacubitril/valsartan had a lower risk of experiencing CV death or HF hospitalization (HR: 0.63, 95% CI 0.31-1.28) or either of its components; CV death (HR: 0.50, 95% CI 0.20-1.26); HF hospitalization (HR: 0.83, 95% CI 0.32-2.16). Both treatment arms share similar demographics, disease characteristics, treatment, and medical history. The safety profile was similar to the overall study population (Ramires et al 2018).

Although this analysis was underpowered and should be interpreted with caution, it suggests that the benefit of sacubitril/valsartan in patients with CCC is consistent with that in the overall study population.

While PARADIGM-HF showed a clear effect of sacubitril/valsartan in the management of HFrEF independently of the underlying etiology (including CCC), considering the unique characteristics of the CCC as compared to other forms of cardiomyopathy, a study specifically in this population is needed.

Therefore, taking into consideration all these facts, this study has been designed to test the hypothesis that sacubitril/valsartan is superior to enalapril in reducing a composite of CV events (CV death or first HF hospitalization) or in causing a greater reduction or lesser increase in NT-proBNP levels at Week 12 in HFrEF participants with CCC.

1.2 Purpose

The purpose of this study is to evaluate the effect of sacubitril/valsartan 200 mg BID compared with enalapril 10 mg BID, in addition to conventional HF treatment, in improving a hierarchical composite of CV events (i.e. CV death or the occurrence of first HF hospitalization) and causing a greater reduction or lesser increase in NT-proBNP (at Week 12 from Baseline) in participants with HFrEF caused by CCC.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objectives	Endpoints
Primary	
To assess whether sacubitril/valsartan is superior to enalapril in improving a composite hierarchical outcome of: a) time to CV death, b) time to first HF hospitalization, c) relative change in NT-proBNP levels between Baseline and Week 12 in participants with HFrEF caused by CCC	The primary endpoint is the hierarchically ordered composite consisting of time to CV death, time to first HF hospitalization, and the relative change from Baseline to Week 12 in NT-proBNP levels
Secondary	
1. To test whether sacubitril/valsartan is superior to enalapril in delaying the time from randomization to first occurrence of hospitalization due to HF or CV death	1. A composite outcome consisting of time from randomization to the occurrence of the first HF hospitalization or CV death
2. To test whether sacubitril/valsartan is superior to enalapril in delaying the time to death from any cause (all-cause mortality)	2. Time from randomization to all-cause mortality
3. To test whether sacubitril/valsartan is superior to enalapril in delaying the time to the first occurrence of resuscitated sudden cardiac arrest or sudden cardiac death	3. Time from randomization to sudden death or resuscitated sudden cardiac arrest
4. To test whether sacubitril/valsartan is superior to enalapril in reducing the number of visits to ER for HF (where intravenous therapy is required)	4. Number of visits to an ER due to HF (where intravenous therapy is required)
5. To test whether sacubitril/valsartan is superior to enalapril in increasing the number of days alive out of the hospital	5. Number of days alive out of the hospital
6. To compare sacubitril/valsartan with enalapril as to their safety and tolerability in participants with CCC	6. Safety and tolerability parameters: a. physical examination (as described in Table 8-2) b. vital signs c. laboratory evaluations d. electrocardiogram e. pregnancy assessment f. adverse events g. serious adverse events h. adverse events of special interest (angioedema, arrhythmia, symptomatic hypotension, hyperkalemia, and renal dysfunction

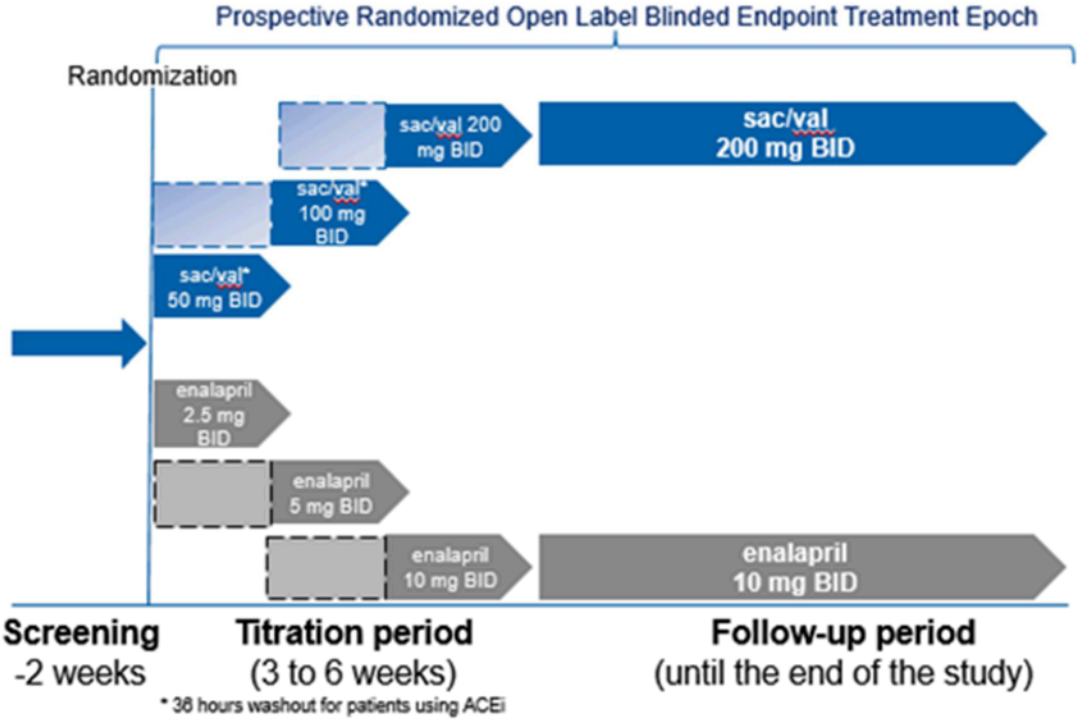
Objectives	Endpoints
Exploratory	
1. To test whether sacubitril/valsartan is superior to enalapril in reducing ventricular fibrillation or sustained ventricular tachycardia needing specific pharmacological, electrical or other treatment	1. Number of ventricular fibrillation or sustained ventricular tachycardia needing specific pharmacological, electrical, or other treatment
2. In the subset of participants with an implantable cardioverter defibrillator (ICD) or CRT-D at randomization: to test whether sacubitril/valsartan is superior to enalapril in reducing anti-tachycardia pacing or shock therapies	2. Number of anti-tachycardia pacing or shock therapies

3 Study design

This is a Phase 4, multinational, multicenter, parallel-group, prospective, randomized, open-label, blinded-endpoint adjudication (PROBE), active-controlled study to demonstrate superiority of sacubitril/valsartan over enalapril in improving a composite of CV events (CV death or first HF hospitalization) or in causing a greater reduction or lesser increase in NT-proBNP levels at Week 12 in participants with HFrEF caused by CCC.

The study will consist of a Screening Epoch, and a Randomized Treatment Epoch consisting of a Titration Period, and a Follow-up Period (Figure 3-1).

Figure 3-1 Study design



Remote procedures

If not possible for study participants to go to the sites to perform study visits , site staff should do all efforts in order to contact the subject for safety reasons in order to confirm subject's safety and occurrence of endpoints and unreported SAEs.

Also IP delivery and blood collection may also be arranged at participant's home at investigator's discretion.

Any study visit or procedure not completed or completed with delays, because of COVID-19 pandemic impact should be registered as a protocol deviation.

3.1 Screening Epoch

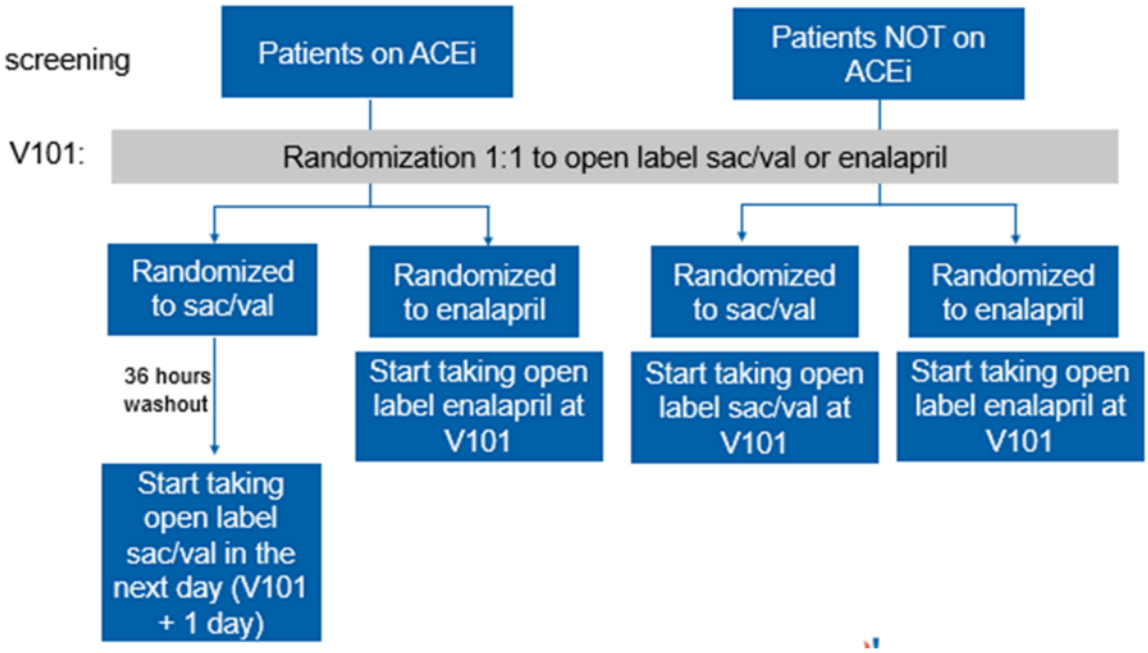
The Screening Visit (Visit 1) will be performed up to 2 weeks before the Randomization Visit (Visit 101) to allow adequate time for the completion of all qualifying screening procedures (Table 8-1). Importantly, the Randomization Visit should occur within 2 weeks of the screening NT-proBNP/BNP test.

Eligible participants who are enrolled in the study will sign the informed consent before any study-related assessments are performed, and continue their baseline medication regimen. Participants must be instructed not to take their prior ACEIs or ARBs on the day of the Randomization Visit. Participants taking ACEIs who are randomized to sacubitril/valsartan will do a 36-hour ACEI washout before they start taking the study drug (the first dose of sacubitril/valsartan will be taken the next day at 36 hours after the Randomization Visit). Participants will discontinue their prior ACEIs or ARBs after randomization.

3.2 Randomized Treatment Epoch

At the Randomization Visit, all participants who fulfill the inclusion criteria and do not meet any exclusion criteria will be randomized to sacubitril/valsartan or enalapril. Those randomized to sacubitril/valsartan who have been receiving treatment with ACEIs must start the study drug only on the next day after the Randomization Visit in order to achieve at least 36-hour washout of ACEIs before taking sacubitril/valsartan (Figure 3-2).

Figure 3-2 Study drug initiation



V101: Visit 101 (Randomization Visit).

Participants must be instructed not to take their previous renin-angiotensin system inhibitors on the day of the Randomization Visit and discontinue those medications after randomization.

3.2.1 Titration Period

For definitions of low and standard dosages of ACEI/ARB, refer to the Glossary of terms. Minimum pre-study total daily doses of commonly used ACEIs and ARBs allowing participants to begin the treatment at Dose Level 2 are shown in Table 3-1.

Upon Randomization, participants will enter a Titration Period, which is based on the conservative arm of the CLCZ696B2228 (TITRATION) study. Dose titration is performed every 3 weeks as follows:

The initial dosage of study drugs during the Titration Period will depend on the treatment the participants have been receiving before Randomization (Table 3-1 and Table 3-2):

- Participants **not currently treated** with ACEI/ARBs and participants treated with **low dosages** (less than 50% of the target dosage) before Randomization will initially be assigned to receive **Dose Level 1** of study drugs for 3 weeks:
  - enalapril 2.5 mg BID or
  - sacubitril/valsartan 50 mg BID
- Participants treated with **standard dosages** (at least 50% of medium or standard ACEI/ARB dosage) of ACEIs/ARBs before Randomization will be assigned to receive **Dose Level 2** of study drugs for 3 weeks:
  - enalapril 5 mg BID or
  - sacubitril/valsartan 100 mg BID

- Participants treated with target dosage of ACEi/ARBs (Table 3-2) before randomization, if randomized to the enalapril arm, do not need to be downtitrated and can enter the study (as per investigator criteria) directly at Dose Level 3 of the titration period:
  - enalapril 10 mg BID
    The independent Clinical Endpoint Adjudication Committee and the clinical study blinded teams from Novartis and BCRI must not have access to this information in order to remain blinded to treatment allocation.

Table 3-1 Minimum pre-study total DAILY doses of commonly used ACEIs and ARBs allowing participants to begin the treatment at Dose Level 2

ACEI	Daily dose	ARB	Daily dose
Benazepril	20 mg	Azilsartan	40 mg
Captopril	100 mg	Candesartan	16 mg
Cilazapril	2.5 mg	Eprosartan	400 mg
Enalapril	10 mg	Irbesartan	150 mg
Fosinopril	20 mg	Losartan	50 mg
Imidapril	10 mg	Olmesartan	10 mg
Lisinopril	10 mg	Telmisartan	40 mg
Moexipril	7.5 mg	Valsartan	160 mg
Perindopril	4 mg		
Quinapril	20 mg		
Ramipril	5 mg		
Trandolapril	2 mg		
Zofenopril	30 mg		

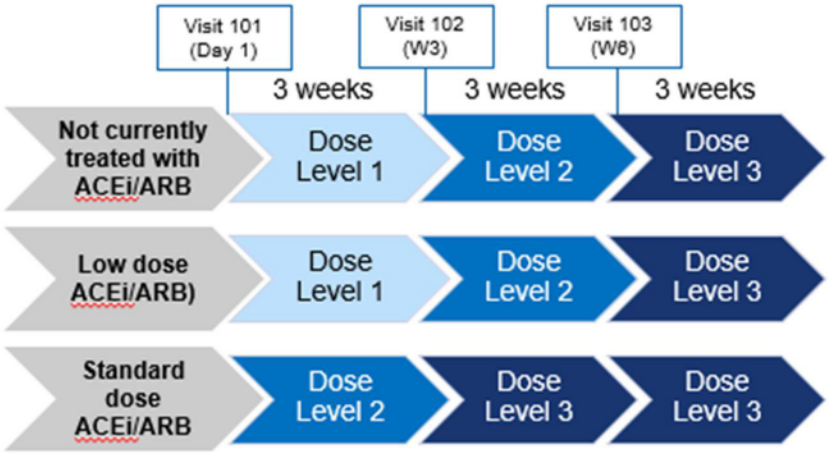
Table 3-2 Minimum pre-study total DAILY doses of commonly used ACEIs and ARBs allowing participants RANDOMIZED TO THE ENALAPRIL arm to begin the treatment at Dose Level 3 (enalapril 10 mg BID)

ACEI	Daily dose	ARB	Daily dose
Benazepril	20 mg	Azilsartan	80 mg
Captopril	150 mg	Candesartan	32 mg
Cilazapril	5 mg	Eprosartan	800 mg
Enalapril	20 mg	Irbesartan	150 mg
Fosinopril	40 mg	Losartan	150 mg
Imidapril	20 mg	Olmesartan	40 mg
Lisinopril	20 mg	Telmisartan	80 mg
Moexipril	30 mg	Valsartan	320 mg
Perindopril	8 mg		
Quinapril	40 mg		
Ramipril	10 mg		
Trandolapril	4 mg		
Zofenopril	60 mg		

After 3 weeks, these dosages will be up-titrated as follows:

- Participants who initially received Dose Level 1 (enalapril 2.5 mg BID or sacubitril/valsartan 50 mg BID) will be treated with Dose Level 2 (enalapril 5 mg BID or sacubitril/valsartan 100 mg BID) for an additional 3 weeks, after which they will be up-titrated again to the target Dose Level 3 (enalapril 10 mg BID or sacubitril/valsartan 200 mg BID)
- Participants who initially received Dose Level 2 (enalapril 5 mg BID or sacubitril/valsartan 100 mg BID) will be up-titrated to the target Dose Level 3 (enalapril 10 mg BID or sacubitril/valsartan 200 mg BID) (Figure 3-3)

Figure 3-3 Study drug titration scheme



Participants treated with target dosage of ACEi/ARBs (Table 3-2) before randomization, **if randomized to the enalapril arm**, do not need to be down titrated and can enter the study (as per investigator criteria) directly at Dose Level 3 of the titration period: enalapril 10 mg BID

In certain circumstances, longer up-titration periods may be required as the Investigator deems necessary. Participants should meet the safety criteria (Table 3-2) before initiation of study drug and during each up-titration stage.

The aim is to achieve the target Dose Level 3 within **6 weeks** after Randomization. However, slower up-titration will be permitted if necessary to manage participant's tolerability.

Investigators should document the reasons for not achieving the target dose during the Week 3 to Week 6 visits.

Participants who cannot tolerate Dose Level 3 will be allowed to stay at Dose Level 1 or 2 as maintenance dose. Dose level adjustments should be based on overall safety and tolerability with special focus on a) symptomatic hypotension, b) any clinically significant decrease in eGFR/increase in creatinine, and c) hyperkalemia (Table 3-2). Treatment guidelines for hyperkalemia and for blood pressure management are provided in Appendix 4 and Appendix 5.

Every attempt should be made to maintain participants on the target dose or the maximally-tolerated dose levels throughout the study. If the participant does not tolerate the target dose, the Investigator should consider adjusting non-disease-modifying background medications (e.g.

diuretics, nitrates, or calcium channel blockers) to rectify the situation before considering down-titration to the next lower dose level.

Table 3-3 Safety monitoring criteria that must be met for dose up-titration

Parameter	Criteria
Blood pressure	No symptomatic hypotension and SBP ≥ 95 mmHg
Renal function	eGFR ≥ 30 mL/min/1.73 m^2 or eGFR reduction < 35% compared to Visit 1
Serum potassium (or equivalent plasma potassium value)	Potassium ≤ 5.4 mmol/L (mEq/L)
Adverse events or conditions	No symptoms suggestive of hypotension or any AEs that preclude up-titration according to the Investigator's judgment

3.2.2 Follow-up Period

After titration, all participants will receive Dose Level 3 of study drugs at the target dosages (sacubitril/valsartan 200 mg BID or enalapril 10 mg BID) if they tolerate them. Dose Level 3 should be maintained until the end of the study.

Participants who no longer tolerate the target dosages at any time during the course of the Follow-up Period may be down-titrated to the nearest lower dosage at the Investigator's discretion.

Before considering down-titrating the dosage of study drug to the nearest lower dose level, the Investigator should consider reducing non-disease-modifying medications (e.g., calcium channel blockers, diuretics, nitrates, and α-blockers) to rectify the situation. Every attempt should be made to re-challenge the participants so that they are kept on the maximal tolerated dose of study drug for as long as possible throughout the Follow-up Period.

If study drug is temporarily discontinued, it should be reintroduced as soon as it is medically justified. Study drug discontinuation for any reason after Randomization, will not constitute withdrawal from the study. Participants are expected to attend all the protocol-specified study visits to perform all assessments as stipulated in the visit schedule, unless they do not want to continue in the study or withdraw consent. For participants who do not wish to continue with the protocol specified assessments, before withdrawn completely from the study, should be offered some modified follow-up, e.g., by less frequents visits, a final in-person visit with telephone follow-up for other planned visits, telephone follow-up alone, follow-up through contact with the primary care physician or through medical records etc.

The study will end when at least 302 events have occurred (CV death or first HF hospitalization) and when all participants have a minimum follow up of 3 months. However, based on the planning assumptions (see Section 12.8) the overall study duration estimated to achieve the 302 events will be approximately 36 months, with a projected recruitment period of approximately 18 months and a follow-up period of 18 months after the enrollment of the last participant.

4 Rationale

4.1 Rationale for study design

This study has a prospective, randomized, open-label blinded-endpoint adjudication (PROBE) design (Hansson et al 1992). Investigators and participants will have full knowledge of the treatment allocation but the independent Endpoint Adjudication Committee will be blinded to treatment allocation.

Blinded end-point evaluation of all of clinical events, which could potentially fulfill the criteria for the primary or secondary endpoints, will be assessed during the study and reported to an independent Clinical Endpoint Adjudication Committee for respective assessment and adjudication.

Blood samples will be obtained to determine changes from Baseline in NT-proBNP.

In order to minimize the potential impact of knowledge of study treatment, **no** aggregate statistical analyses performed during the study will include treatment assignment. The study Steering Committee and the study team from Novartis and the vendor ARO (the Brazilian Clinical Research Institute) will be blinded to the study treatment assignment and only the (DMC) will see data with treatment assignment during the study. The analyses for their safety monitoring meetings (which will occur every 6 months) will be performed by an independent statistician working with the DMC.

The slow Titration Period is similar to that of the conservative arm of the TITRATION study. Patients with CCC are at high risk of hypotension, and slow titration is necessary to ascertain tolerability to the target dosages of sacubitril/valsartan and enalapril, and to minimize the risk of SAEs and participant dropouts.

The 36-hour washout is required for participants in previous use of an ACEI and randomized to sacubitril/valsartan to minimize the risk of angioedema, which potentially increases with simultaneous inhibition of ACE and NEP.

4.2 Rationale for dose/regimen and duration of treatment

The 200 mg BID target dosage for sacubitril/valsartan for this study was based primarily on the superior efficacy and safety results of sacubitril/valsartan 200 mg compared to enalapril 10 mg in the PARADIGM-HF study. Further, biomarker analysis and modeling indicate that this dose of sacubitril/valsartan delivers approximately 90% of its maximal NEP inhibition. The BID dosing schedule is considered necessary for sustained NEP inhibition over a 24-hour period andit is also anticipated to reduce the incidence of hypotension, compared with a once daily regimen, particularly in elderly participants.

4.3 Rationale for choice of comparator

Treatment guidelines have established ACEI treatment as the standard of care for blockade of the renin-angiotensin-aldosterone system in participants with HFrEF unless they are intolerant.

Although there are no prospective studies testing the effects of standard treatment in participants with CCC, the guidelines recommend treating these participants with the same medications

indicated for HF due to other etiologies (Andrade et al 2011, Bocchi et al 2012, Nunes et al 2018).

High doses of enalapril increase LVEF, improve quality of life, and decrease serum BNP and chemokines in participants with Chagas' disease with HF (Szajnbok et al 1993). The 10-mg BID dosage has been selected as the target dose based on its ability to reduce the risk of death or hospitalization as demonstrated in the SOLVD studies (SOLVD 1991, SOLVD 1992).

4.4 Purpose and timing of interim analyses

No formal efficacy interim analysis is planned for the study.

4.5 Risks and benefits

Overall, the safety profile of sacubitril/valsartan in patients with HFrEF is similar to or better than that of the standard of care, including enalapril (see sacubitril/valsartan Investigator's Brochure). The low rate of discontinuations observed suggests that most of the AEs can be managed with clinical measures. Sacubitril/valsartan has a well-characterized safety profile and is generally safe and well tolerated in patients with HF.

The overall benefit-risk balance of sacubitril/valsartan has been positive for the treatment of HF (NYHA Class II-IV) in patients with systolic dysfunction, and has been considered acceptable for clinical development of treatments of other CV indications (see sacubitril/valsartan Investigator's Brochure).

The risk to participants in this study will be minimized by compliance with the eligibility criteria and study procedures, and by close clinical monitoring.

4.5.1 Risks

Experience from 4203 patients treated with sacubitril/valsartan and 4229 patients treated with enalapril in the PARADIGM-HF study indicate that the major risks associated with both treatments are renal dysfunction, hyperkalemia, and hypotension (Table 4-1).

Table 4-1 Rate of events per treatment during the Follow-up Period of the PARADIGM-HF study

Event	Sacubitril/valsartan (n = 4203)	Enalapril (n = 4229)
	n (%)	n (%)
Renal dysfunction	426 (10.14)	487 (11.52)
Hyperkalemia	488 (11.61)	592 (14.0)
Hypotension	740 (17.61)	506 (11.97)

n: number of participants

Results from the TITRATION study indicate that more participants who were naïve to previous ACEI or ARB therapy or on low doses of these agents were able to achieve and maintain sacubitril/valsartan 200 mg when up-titrated slowly (over 6 weeks).

In this study, the risk of renal dysfunction and hypotension will be mitigated by appropriate slow up-titration of the study drugs. Participants with CCC are at higher risk of hypotension because of the early involvement of both ventricles. Therefore, the titration will be slow to

decrease the risk of hypotension. The risks will be further mitigated by appropriate application of the exclusion criteria. Participants will be excluded if they have an eGFR < 30 mL/min/1.73 m^2.

Drug-to-drug interactions are known to occur with the concomitant use of ACEs, ARBs, neutral endopeptidases, and renin inhibitors. Participants will be provided with study drug instructions and their prior and concomitant medication use will be reviewed at Screening and at all subsequent visits.

Confirmed cases of angioedema were observed in the randomized treatment epoch of PARADIGM-HF, with both sacubitril/valsartan (19 [0.5%] of 4203 participants) and enalapril (10 [0.2%] of 4229 participants). The risk of developing angioedema is increased in participants who take an ACEI in addition to sacubitril/valsartan. To decrease this risk, participants using ACEIs will be required to undergo a 36-hour washout before they start sacubitril/valsartan to minimize the potential drug interaction.

The study procedures and assessments are either non-invasive or minimally invasive (venipuncture for blood draws) and are considered to pose low risk.

4.5.2 Benefits

All participants will receive active treatment for HF, which reduces the risk of death and hospitalizations.

Study assessments and frequent visits will assure close monitoring of participants and information that may benefit future HF patients.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. 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.

5 Population

The study participants will consist of men and women aged 18 years or older with NYHA Class II-IV HFrEF (LVEF ≤ 40%) caused by Chagas' disease. The target projected sample size is approximately 900 participants (450 in each arm). It is estimated that approximately 1800 participants will be screened at up to approximately 100 study sites because a screen failure rate of approximately 50% is anticipated, based on previous experience in other HF studies.

5.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed
2. Male or female ≥ 18 years of age
3. Diagnosis of NYHA Class II-IV HFrEF established by:
   a. LVEF ≤ 40% within 12 months prior to Visit 1 made by any local measurement using echocardiography, MUGA, CT scanning, MRI, or ventricular angiography, provided no subsequent measurement above 40% AND
   b. NT-proBNP ≥ 600 pg/mL (or BNP ≥ 150 pg/mL) at Visit 1 OR
   c. NT-proBNP ≥ 400 pg/mL (or BNP ≥ 100 pg/mL) at Visit 1 and a hospitalization for HF within the last 12 months

   NOTE: An echocardiography is allowed to be performed during Screening only if there is no previous ejection fraction measurement (within 12 months)

   Chagas' disease diagnosis confirmed by at least two different serological tests for anti-Trypanosoma cruzi based on different principles or with different antigenic preparations, such as: enzyme-linked immunosorbent assay [ELISA], indirect immunofluorescence [IFI], indirect hemagglutination [IHA], western blot (WB), chemiluminescent immunoassay (CLIA). If documented history is not available, the tests may be performed during the screening

5.2 Exclusion criteria

Patients fulfilling any of the following criteria will not be eligible for inclusion in this study. The Investigator may apply no additional exclusions, in order to ensure that the study population is representative of all eligible participants.

1. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer
2. History of hypersensitivity or allergy to any of the study drugs or their excipients, drugs of similar chemical classes, ACEIs, ARBs as well as known or suspected contraindications to the study drugs
3. Patients with history of suspected or proven angioedema or unable to tolerate ACEIs, ARBs or ARNI (e.g., due to cough, hypotension, renal dysfunction, hyperkalemia)
4. Known hepatic impairment (as evidenced by total bilirubin > 3.0 mg/dL or increased ammonia levels, if performed), or history of cirrhosis with evidence of portal hypertension such as esophageal varices
5. Use of sacubitril/valsartan in the past 3 months
6. Patients requiring continuous intravenous inotropic therapy or with indication of advanced support intervention for HF:
   a. already on list for a heart transplantation
   b. with current indication of left ventricular assist device, or CRT
7. Systemic systolic blood pressure lower than 95 mmHg or symptomatic hypotension at Screening (Visit 1)

8. Serum potassium > 5.2 mmol/L at Screening (Visit 1)
9. Presence of other cardiac conditions:
    a. Previous cardiac surgery
    b. Heart failure where, in the Investigator's judgement, there is a possible alternative primary etiology e.g., due to coronary artery disease, valve disease, congenital heart disease, or other causes.
    c. Untreated arrhythmia or serious conduction disease e.g., bradyarrhythmias, atrial fibrillation with rapid ventricular response, second or third degree atrioventricular block, etc.
    d. Primary uncorrected valvar pathology like moderate to severe aortic stenosis, mitral stenosis and primary mitral regurgitation
    e. Planned organ transplantation (or in listing for transplantation), planned cardiac or other major surgery (including ventricular assist device implantation)
10. eGFR < 30 mL/min/1.73 m^2 of body surface area at Screening (Visit 1)
11. Clinical conditions or systemic diseases limiting proper patient participation:
    a. systemic infection
    b. alcohol/drug abuse
    c. non-treated/uncontrolled thyroid dysfunction
    d. un-controlled diabetes
    e. chronic pulmonary embolism
    f. patient is too sick to participate in decision-making
    g. end-stage systemic disease and/or palliative care for terminal situation
    h. poor or non-adherence to medical treatment
12. Severe gastrointestinal form of chronic Chagas' disease (demonstrated megaesophagus and/or important megacolon, e.g.: with compromised oral intake or surgical indication).
13. Pregnant or nursing (lactating) women
14. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study drug. Highly effective contraception methods include:
    - total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking study drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
    - male sterilization (at least 6 months prior to Screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant
    - use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study drugs.

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least in the previous 6 weeks. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of childbearing potential.

15. History of malignancy of any organ system (other than localized basal or squamous cell carcinoma of the skin or localized prostate cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
16. Current confirmed COVID19 infection
17. Past COVID19 infection with persistent symptom burden suspected due to COVID19 (persistent symptoms may include, but are not limited to, continued cough, breathing difficulty, muscle/joint aches, and gastrointestinal symptoms from the time of COVID19 infection onward)

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Investigational/control drug (name and strength)	Pharmaceutical dosage form	Route of administration	Supply type	Sponsor (global or local)
sacubitril/valsartan 50 mg	Film-coated tablets	Oral	Open label participant packs	Sponsor (local)
sacubitril/valsartan 100 mg	Film-coated tablets	Oral	Open label participant packs	Sponsor (local)
sacubitril/valsartan 200 mg	Film-coated tablets	Oral	Open label participant packs	Sponsor (local)
enalapril 5 mg	Tablets	Oral	Open label participant packs	Sponsor (local)
enalapril 10 mg	Tablets	Oral	Open label participant packs	Sponsor (local)
sacubitril/valsartan (LCZ696) in dose levels of 50 mg, 100 mg, and 200 mg are equivalent to sacubitril/valsartan 24/26 mg, 49/51 mg and 97/103 mg, respectively				

Titration Period

After Screening and a 36-hour washout (for participants randomized to sacubitril/valsartan previously treated with ACEIs), all eligible participants will enter a Titration Period, during which they will be treated with sacubitril/valsartan (50 mg or 100 mg BID) or enalapril (2.5 mg or 5 mg BID).Participants entering the study and being treated with target dosage of ACEi/ARBs (Table 3-2) before randomization, if randomized to the enalapril arm, do not need to be down-titrated and can enter the study directly at Dose Level 3 of the titration period: enalapril 10 mg BID.

The study drugs will be provided as follows:

- enalapril 5 mg tablets to be split in half (enalapril Dose Level 1)
- enalapril 5 mg tablets (enalapril Dose Level 2)
- enalapril 10 mg tablets or 2 tablets of enalapril 5 mg (enalapril Dose Level 3)
- sacubitril/valsartan 50 mg film-coated tablets (sacubitril/valsartan Dose Level 1)
- sacubitril/valsartan 100 mg film-coated tablets (sacubitril/valsartan Dose Level 2)
- sacubitril/valsartan 200 mg film-coated tablets (sacubitril/valsartan Dose Level 3)

Participants will be required to take enalapril or sacubitril/valsartan BID at the corresponding dose level in addition to their conventional concomitant drug therapy (except for ACEIs or ARBs, which will be substituted by the study drug).

Follow-up Period

The study drugs will be provided as follows:

- enalapril 10 mg tablets or 2 tablets of enalapril 5 mg (enalapril Dose Level 3)
- sacubitril/valsartan 200 mg film-coated tablets (sacubitril/valsartan Dose Level 3)

Based on the defined safety and tolerability criteria, participants who do not tolerate the target dosage (sacubitril/valsartan 200 mg BID or enalapril 10 mg BID) will be titrated down to the lower dose level, at the Investigator's discretion.

Sacubitril/valsartan and enalapril will be provided in blister packs or bottles.

6.1.2 Additional study treatments

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

6.1.3 Treatment arms

Participants eligible for Randomization at Visit 101 will be assigned to one of the following treatment arms in a 1:1 ratio:

- sacubitril/valsartan 200 mg BID
- enalapril 10 mg BID

6.1.4 Treatment duration

The study will end when at least 302 events have occurred (CV death or first hospitalization for HF) and when all participants have a minimum follow up of 3 months. Based on the planning assumptions (see Section 12.8) the overall study duration estimated to achieve the 302 events will be approximately 36 months, with a projected recruitment period of approximately 18 months and a follow-up period of 18 months after the enrollment of the last participant.

6.2 Other treatments

No additional treatment is included in this study.

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant is enrolled in the study must be recorded on the appropriate eCRF.

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

6.2.1.1 Medications known to raise potassium levels

Potassium-sparing diuretics, potassium supplements and any other medications known to raise potassium levels should be used with caution while the participant is receiving the study drug due to the increased possibility of occurrence of hyperkalemia. The Investigator is encouraged to assess participants' potassium levels regularly, especially in those who are receiving these medications.

6.2.1.2 Phosphodiesterase-5 inhibitors

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

6.2.1.3 HMG-CoA reductase inhibitors

Caution is recommended when co-administering sacubitril/valsartan with atorvastatin or other statins because of the potential to raise its plasma level. No meaningful increase in statin-related AEs was observed when sacubitril/valsartan was used concomitantly with statins in the PARADIGM-HF (Streefkerk et al 2017) study. No dose adjustments are currently proposed for atorvastatin or other statins when co-administered with sacubitril/valsartan, Investigators should treat their participants with statins based on their best clinical judgement and local treatment guidelines. Diligent monitoring and reporting of statin-related AEs should also be performed.

6.2.2 Prohibited medication

Concomitant use of open-label ACEIs, ARBs, commercially available sacubitril/valsartan, or renin inhibitors is strictly prohibited while the participant is receiving study drug in any study epoch.

If the Investigator believes that use of one of these drugs is necessary, then study drug must be discontinued. Attention should be given to guarantee at least 36-hour washout when switching from ACEI to sacubitril/valsartan or vice-versa. If the participant is receiving enalapril and will switch to sacubitril/valsartan the enalapril must be stopped ≥ 36 hours prior to initiating sacubitril/valsartan. If the participant is receiving sacubitril/valsartan and will switch to any ACEI, the sacubitril/valsartan must be stopped ≥ 36 hours prior to initiating the ACEI. If study drug is to be re-started, the open-label ACE inhibitor or sacubitril/valsartan must also be stopped ≥ 36 hours prior to re-initiating study drug. ARBs or a direct renin inhibitor should be stopped prior to resuming study drug.

Concomitant administration of renin inhibitors, such as aliskiren, is prohibited.

6.2.3 Rescue medication

Participants may receive ACEIs, ARBs, or sacubitril/valsartan during the study **ONLY** if the study drug has been discontinued either temporarily or permanently (see Section 6.2.2 for information on the required washout).

The use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies/Dose Administration Record eCRF page.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is uniquely identified in the study by a combination of his/her study site number and participant number. The study site number is assigned by the vendor ARO to the study site. Upon signing the model informed consent form, the participant is assigned a participant number by IWRS.

At each study site, the first participant is assigned participant number 1, and subsequent participants are assigned consecutive numbers (e.g., the second participant is assigned participant number 2, the third participant is assigned participant number 3). The Investigator or his/her staff will contact the IWRS and provide the requested identifying information for the participant to register them into the IWRS.

To eliminate any manual transcription errors, IWRS will be programmed to electronically transfer the participant data and study identification number to create the participant's case book within the EDC system. Once assigned to a participant, the participant number will not be reused. If the participant fails to be randomized for any reason, the IWRS must be notified within 2 days that the participant was not randomized. The reason for not being randomized will be enter on Screening phase disposition eCRF.

In addition, the screening log should be completed for all participants. Additional information to be collected on screening failures is described in Section 8.1.1.

6.3.2 Treatment assignment, randomization

At Visit 101, after confirming that the participant fulfills all the inclusion/exclusion criteria, the Investigator or his/her delegate will log in to IWRS a second time in order to randomize the participant to one of the treatment arms. The number that was assigned to the study site and participant will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and Investigator staff. A participant randomization list will be produced by the IWRS provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of the vendor ARO using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

The randomization scheme for participants will be reviewed and approved by a member of the Novartis Randomization Office.

6.4 Treatment blinding

Treatment will not be blinded to participants, Investigator staff, and persons performing the assessments. However, treatment will be blinded to the clinical trial team to avoid any bias during the study. Blinding of the DMC and the Clinical Endpoint Adjudication Committee are described in separate documents as outlined in Section 10.2.2 and Section 10.2.3.

6.5 Dose escalation and dose modification

Every attempt should be made to maintain participants on the target dose level for as long as possible throughout the study. However, if the participant does not tolerate the target dosage of study drug (Dose Level 3), the Investigator should consider whether non-disease-modifying medication (e.g., calcium channel blockers, diuretics, nitrates, α-blockers) can be reduced to rectify the situation, before reducing the dose of the study drug to the nearest lower dose level.

In addition, the Investigator may adjust doses of disease-modifying medications if it is believed that they are the most likely cause of the adverse effect. If adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern, the Investigator may down-titrate the dose of the study drug to the nearest lower level up to complete withdrawal of the study drug.

The participant should be re-challenged with the higher dose when the Investigator feels it is appropriate to do so per the directions provided below in this section. If needed, the study drug may be stopped completely, but the participant should continue to attend the study visits and be followed until the completion of the study. Ultimately, the goal is to keep the participant on the highest possible dose level for as long as possible and to follow the participant in the study as long as possible.

Dose level adjustments should mainly be based on overall safety and tolerability with special focus on:

a. hyperkalemia
b. symptomatic hypotension and
c. clinically significant decrease in eGFR/increase in serum creatinine

6.5.1 Dose modifications

If adjustment of concomitant medications per the guidance provided above does not rectify the situation, the Investigator may consider adjusting the study drug according to the following instructions.

6.5.1.1 Dose adjustments during the Follow-up Period

If necessary, participants should be down-titrated to the nearest lower dose level which may be continued for a recommended time of 1 to 4 weeks before they are re-challenged with the nearest higher dose level. For example, participants with tolerability problems at the target dosage (Dose Level 3) should receive the study drug at Dose Level 2 for 1 to 4 weeks. Then, they should be re-challenged by up-titrating back to Dose Level 3 (see Table 6-2). If the re-challenge is not successful, the participants should be maintained in the tolerated dose level for 1 to 4 weeks and then re-challenged again.

If the tolerability issues are not alleviated despite down-titration by one dose level, the Investigator may lower the dose further to the nearest lower level for 1 to 4 weeks, and even temporarily withdraw the study drug. Once stable, participants should be re-challenged with up-titration to the nearest higher dose level every 1 to 4 weeks in an attempt to bring them gradually back to the target Dose Level 3.

Investigators may choose the nearest dose level for down- or up-titration according to their judgment. The IWRS should be contacted to register any changes in the participant's dose level, including in cases of temporary and permanent withdrawal of the study drug, and to obtain the medication numbers of the study drug supplies required for the new study drug dose level.

In some instances, according to the safety and tolerability criteria and the Investigators' judgment, Dose Levels 1 or 2 could be maintained if they consider that the participant's condition would not allow any further up-titration to the target Dose Level 3. In this case, it would be acceptable to maintain the participant at Dose Level 1 or Dose Level 2, whichever is the higher tolerated dose level.

6.5.1.2 Study drug restart after temporary treatment interruption

Study drug should be reintroduced in those participants who temporarily discontinue it as soon as medically justified in the opinion of the Investigator.

Once the Investigator considers the participant's condition is appropriate for receiving the study drug, the Investigator should re-start the participant on the study drug at the most appropriate and allowable dose level per his/her medical judgment. If tolerated, the participant should be up-titrated up to Dose Level 3 every 1 to 4 weeks, as per the Investigator's judgment. Participants re-started on the study drug will retain their original randomization and study identification numbers. Should the participants not tolerate the re-start dose level, they may be down-titrated again (if appropriate) or the study drug discontinued again and a new attempt to

up-titrate or reintroduce the study drug could be considered by the Investigator as soon as medically justified in his/her medical judgment.

Study visits should occur as close as possible to the time points indicated in Table 8-1. The timeframe between the regular visits should be maintained as scheduled, irrespective of the number of unscheduled visits that may be performed in between, according to the visit and time schedule described in Table 8-1. For example, if the participant's treatment needs to be adjusted between Visit 109 and Visit 110, Visit 110 will still be planned 6 months after Visit 109, irrespective of the number of unscheduled visits that may have occurred between these 2 visits or the additional period that the medication pack dispensed could have covered.

Any changes in dose level, including temporary/permanent withdrawal or restart of the study drug, must be recorded on the Dosage Administration Record eCRF page and registered in the IWRS.

In case of pregnancy discovered during Screening the participant must not be randomized and be discontinued from the study. If discovered during the Titration or Follow-up Period, the participant should be instructed to stop taking study drug immediately. Study drug intake should be resumed as soon as possible after the completion of the pregnancy and lactation period. Meanwhile, the participant should continue to attend scheduled study visits.

See Section 10.1.4 for further details on pregnancies and reporting guidelines. These changes must be recorded on the Dosage Administration Record eCRF page.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

All doses of study treatment administered will be recorded on the appropriate Dosage Administration Record eCRF page. Participant compliance with study treatment should be assessed by qualified study site personnel at each study visit using the study kits and documentation regarding study treatment dispensation and administration.

Compliance will be assessed by the Investigator and/or study personnel at each visit using tablet counts and information provided by the caregiver. This information should be captured in the source document at each visit. Participant compliance should be at least 80% during the Titration and Follow-up Period. The Investigator and/or study personnel will counsel the participant if compliance is below 80%. Study drug accountability will also be determined by the study site monitor while performing routine study site visits and at the completion of the study.

The duration of study drug exposure will be calculated based upon the start and stop dates recorded in the eCRF.

The Investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the Investigator if he/she is unable for any reason to take the study treatment as prescribed.

6.6.2 Emergency breaking of assigned treatment code

Not applicable.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under Section 6.1.1. A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the participant by contacting the IWRS and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the participant, study site personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 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 study site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The Investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during study site visits or remotely and at the completion of the study. Participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to ARO.

6.7.2 Instruction for prescribing and taking study treatment

The ARO will supply the Investigators with all medications for the whole course of the study. Participants will be provided with medication packs containing study drug corresponding to their assigned treatment arm and dose level, sufficient to last until the next scheduled visit.

Table 6-1 and Table 6-2 summarize the study drugs that will be taken during each phase of the Follow-up Period.

Table 6-1 Study drug dispensed during the Titration Period

Dose Level	sacubitril/valsartan (BID)	Enalapril (BID)
1	50 mg	2.5 mg (5.0 mg tablet to be split in half)
2	100 mg	5 mg
3	200 mg	10 mg or two 5 mg tablets

Table 6-2 Study drug dispensed during the Follow-up Period

Dose Level	sacubitril/valsartan (BID)	Enalapril (BID)
1	50 mg	2.5 mg (5.0 mg tablet to be split in half)
2	100 mg	5 mg
3[a]	200 mg	10 mg or two 5 mg tablets

[a] This dose level must be maintained for as long as possible. If down-titration is necessary due to side effects, the participant should be re-challenged as soon as medically possible as per Investigator's judgment.

Participants will be instructed to take their morning dose of study drug at approximately 08:00 h (8 AM) and their evening dose at approximately 19:00 h (7 PM). The study drugs should be taken with a glass of water with or without food. When participants miss any study drug dose, they should take it as soon as possible, unless it is close to the following scheduled dose. In this case, the participant should skip the missed dose and return back to the regular study drug administration schedule.

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

All kits of study treatment assigned by the IWRS will be recorded in the IWRS.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participant's representative gives consent (if allowed according to local requirements), the participants must be informed about the study to the extent possible given their understanding. If the participants are capable of doing so, they 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 participant source documents.

ARO will provide to Investigators in a separate document a proposed model informed consent form that complies with the International Conference on Harmonization (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 ARO/Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator notification or an aggregate safety finding. New information might require an update to the informed consent and must be discussed with the participant.

Women of childbearing potential must be informed that taking the study treatment may involve unknown 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.

A copy of the approved version of all consent forms must be provided to ARO after IRB/IEC approval.

8 Visit schedule and assessments

Assessment schedule lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit 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 AEs and concomitant medications recorded on the eCRF.

Table 8-1 Assessment schedule events

		Titration Period				Follow-up Period *							
Visit number	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108** [a]	**109**	**110**	**111 112...** [f]	**199 EOS**
Time of visit (Day [D], Week [W], Month [M])	**SC**	**D1**	**W3**	**W6**	**W9**	**W12**	**M4**	**M8**	**M12**	**M18**	**M24**	**M30 M36...** [f]	
Inclusion/exclusion criteria	X	X											
Informed consent	X												
Randomization		X [b]											
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Demographics, medical history	X												
Physical examination [c]	S	S	S	S	S	S	S	S	S	S	S	S	S
Height	X												
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
NYHA class (HF signs & symptoms)	X	X	X	X	X	X	X	X	X	X	X	X	X
Abbreviated chemistry [d]	S		S	S	S	S	S	S	S	S	S	S	S
Serum/urine pregnancy tests [e]	S	S	S	S	S	S	S	S	S	S	S	S	S
Dispense study medication		X	X	X	X	X	X	X	X	X	X	X	X
Study drug accountability			X	X	X	X	X	X	X	X	X	X	X
HF and CV medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X
Record HF hospitalizations			X	X	X	X	X	X	X	X	X	X	X
NT-proBNP	(X) [g]	X [h]				X [h]		X [k]					

		Titration Period				Follow-up Period *							
Visit number	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108 [a]**	**109**	**110**	**111 112...[f]**	**199 EOS**
Time of visit (Day [D], Week [W], Month [M])	**SC**	**D1**	**W3**	**W6**	**W9**	**W12**	**M4**	**M8**	**M12**	**M18**	**M24**	**M30 M36...[f]**	
Twelve-lead ECG	X												X
Chagas diagnosis test [i]	(X)												
Echocardiography [j]	(X)												
Biomarkers [k]		X		X				X					
Holter monitoring [l]		X						X					
Magnetic resonance imaging [m]		X						X					

EOS: end of study, SC: screening (Day -14 to Day -1) X = assessment to be recorded on clinical data base

S = assessment to be recorded on eSource/source documentation only

* If the study is extended, Visits 113, 114 and so forth to be performed at the same intervals and with same measurements as at visits 109, 110, and so forth.

** In case of Public Health emergency as declared by Local or Regional authorities (i.e. pandemic) and participants are unable for complete study visits at the site, site staff should do all the efforts to collect at least safety information from the participants by phone in order to confirm unreported SAEs. Also IP delivery at participant's home may also be arranged in order to ensure treatment continuity.

a) Participants should be assessed every 6 months until the end of study.

b) Participants randomized to sacubitril/valsartan who have been receiving treatment with ACEIs must start the study drug only on the next day after the Randomization Visit, considering at least 36 hours after the last ACEI dose taken.

c) A complete physical examination is required at Visits 1, and yearly thereafter until Visit 199 (End-of-study Visit). Short physical examinations will be performed at interim visits

d) Hematology, renal function (blood urea nitrogen, creatinine, serum potassium, Na, Cl), liver function (total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase), and glucose. Local laboratories will analyze all specimens collected

e) In women with childbearing potential, serum and urine pregnancy tests will be performed locally. Serum pregnancy test to be performed at Visit 1 and EOS. Urine pregnancy tests will be done monthly (including at the schedule visits). If serum pregnancy test is positive during the screening and on a confirmatory serum β-hCG test, the participant must not be randomized and must be discontinued from the study. After randomization (Visit 101) a positive urine pregnancy test requires immediate interruption of study drug and confirmation by serum pregnancy test. If positive upon confirmation test, the participant must discontinue study drug until after the pregnancy and lactation period. Further details on the monthly urine pregnancy test are provided in the manual of operations.

f) The visits will occur every 6 months until the EOS and will be sequentially numbered.

g) Local measurement

		Titration Period				Follow-up Period *							
Visit number	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108** [a]	**109**	**110**	**111 112...** [f]	**199 EOS**
Time of visit (Day [D], Week [W], Month [M])	**SC**	**D1**	**W3**	**W6**	**W9**	**W12**	**M4**	**M8**	**M12**	**M18**	**M24**	**M30 M36...** [f]	

h) Central lab

i) Confirmation for Chagas diagnosis tests with 2 different serological tests are allowed to be performed during Screening only if there is no documented historical diagnosis.

j) Qualifying LVEF measurements/documentation will be based on any local measurement (using echocardiography, MUGA, CT scanning, MRI, or ventricular angiography) performed ≤ 12 months prior to Visit 1. An echocardiography is allowed to be performed during Screening only if there is no previous ejection fraction measurement (within 12 months).

k) For participants included in the biomarkers additional assessment, blood samples will be collected at Randomization, Week 6 and Month 8 as described in the laboratory manual. The samples will be processed by a central laboratory and then shipped to and stored in the Novartis repository. For participants included in the biomarkers assessment after the baseline visit, samples can be collected according to detailed in the lab manual.

l) For participants in the Holter monitoring additional assessment

m) For participants in the MRI additional assessment

8.1 Screening

8.1.1 Information to be collected on screening failures

Participants who sign the model informed consent form and subsequently are found to be ineligible prior to randomization will be considered screen failures. The reason for screen failure should be recorded on the appropriate eCRF. The demographic information, informed consent, and inclusion/exclusion pages must also be completed for screen failures. No other data will be entered into the clinical database for screen failures, unless the participant experienced an SAE during the screening phase (see Section 10.1.3 for reporting details). If the participant fails to be randomized, the IWRS must be notified within 2 days.

Participants who are randomized and fail to start treatment, e.g., randomized in error, will be considered early terminators. The reason for early termination should be recorded on the appropriate eCRF.

Reporting of SAEs during the Screening Epoch should be followed as described in Section 10.1.2. The Adverse Events eCRF page should be completed for any SAEs that occur during the Screening Epoch.

Potential AEs and hospitalizations that are not SAEs which may have occurred from the time of signing the informed consent until the time of failed screening will be followed by the Investigator and collected only in the source data.

If a participant discontinues prior to Randomization, the IWRS provider should be notified, and the reason for the participant not being randomized entered on the Screening Epoch Disposition eCRF page. The screening visit date, the Demography eCRF page, the Informed Consent eCRF page, and the Inclusion/Exclusion eCRF page must be completed.

The Withdrawal of Consent eCRF page must be completed if consent is withdrawn during the Screening Epoch before the participant is randomized.

Investigators will have the discretion to record abnormal test findings on the Medical History eCRF page whenever, in their judgment, the test abnormality occurs before the informed consent is signed.

Re-screening

Participants who enter Screening, but are determined not to be eligible to be randomized will be considered screen failures. Investigators may consider re-screening the participants at a later time if they believe that their condition has changed and they may potentially be eligible. In this case, new participant numbers will be allocated to the participants and they will need to have Visit 1 again.

Participants may be re-screened up to 2 times. A minimum of 2 weeks must elapse between re-screenings. Participants must provide new written informed consent each time they are re-screened.

8.2 Participant demographics/other baseline characteristics

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

Demographics and baseline characteristics data to be collected on all participants include date of birth (according to local laws and regulations), age, sex, race, ethnicity, and source of participant referral.

Relevant medical history/current medical condition data include data until the first administration of study drug. Where possible, diagnoses will be recorded, and not symptoms. HF medications and other CV medications will be recorded in eCRFs separate from other medications. Likewise, detailed HF history and other relevant CV medical history will be recorded on eCRFs separate from other medical history.

8.2.1 Smoking history

The current and/or previous use of tobacco products will be recorded, as well as the estimated number of pack-years based on the approximate consumption per year. Non-smokers will be advised not to start smoking during the study.

8.2.2 Relevant medical history/current medical conditions

Relevant medical history and current medical conditions prior to signing of the informed consent will be recorded in the Medical History eCRF page. Whenever possible, diagnoses and not symptoms will be recorded.

Significant findings that are observed after the participant has signed the model informed consent form and that meet the definition of an AE must be recorded in the Adverse Event eCRF page.

8.2.3 Prior and concomitant medications

Concomitant medications and prior medications taken within the 6 months preceding study enrollment will be captured at the Screening Visit, and updated at the Randomization Visit.

8.3 Efficacy

8.3.1 Time from randomization to CV death, or time to the first HF hospitalization, or relative change from Baseline to Week 12 in NT-proBNP

Time to CV death, time to first HF hospitalization, and the relative change in NT-proBNP between Baseline and Week 12 will be determined.

The analysis will be done in a hierarchical order: time to CV death (worst category; earlier time to CV death is unfavorable), time to first HF hospitalization (second worst category; earlier time to HF hospitalization is unfavorable) and the relative change from Baseline to Week 12 in NT-proBNP (best category; more reduction or less increase). In order to differentiate the response in NT-proBNP, the difference needs to be +/- 25%.

This margin was chosen based on PARADIGM-HF data, where a 25% reduction in NT-proBNP was associated with a 15% hazard reduction for the occurrence of a first HF hospitalization or CV death, therefore, it can be considered clinically meaningful, i.e., a 'winner' in an NT-proBNP based comparison is only declared if the relative change of NT-proBNP from Baseline differs for more than 25% between two participants (more reduction or less increase).

8.3.2 Time from randomization to the first occurrence of a composite of CV events

The time to the first occurrence of the composite of HF hospitalization or CV death will be determined.

8.3.3 Time from randomization to all-cause mortality

The time to all-cause mortality will be determined.

8.3.4 Time from randomization to sudden death or resuscitated sudden cardiac arrest

The time to sudden death or resuscitated sudden cardiac arrest will be determined.

8.3.5 Number of visits to an ER due to HF

The rate of visits to an ER due to HF (where intravenous therapy is required) will be determined.

8.3.6 Number of days alive out of the hospital

The number of days alive out of the hospital will be determined.

8.3.7 Number of ventricular fibrillation or sustained ventricular tachycardia needing specific pharmacological, electrical or other treatment

The number of ventricular fibrillation or sustained ventricular tachycardia needing specific pharmacological, electrical, or other treatment will be determined.

8.3.8 Number of anti-tachycardia pacing or shock therapies

This will be determined in a subset on a subset of participants who have an ICD or CRT-D at Randomization.

8.3.9 Appropriateness of efficacy assessments

The measurements are standard for the type of study being performed.

8.4 Safety

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 Assessments and specifications

Assessment	Specification
Physical examination	A complete physical examination will be performed at Visit 1 and at yearly intervals thereafter until the End-of-study Visit. It will include the check of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities, vascular and neurological exploration. If indicated based on medical history and/or symptoms, exams of rectum, external genitalia, breast, and pelvic will be performed. A short physical examination will be performed, except where a complete physical examination is required (see Table 8-1) and will include the check of general appearance and vital signs (blood pressure and pulse). Information about all physical examinations must be present in the source documentation at the study site. Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions eCRF page. Significant findings made after the start of study drug which meet the definition of an AE must be recorded on the Adverse Events eCRF page.
Vital signs	Vital signs will be assessed at every visit and will include sittingmeasurements of blood pressure and pulse. Blood pressure will be measured on the non-dominant arm after 5 minutes of rest using a standard sphygmomanometer with an appropriate size cuff. Normal blood pressure will be defined as systolic pressure of 90 to < 120 mmHg, and diastolic blood pressure of 60 to < 80 mmHg under the measurement conditions outlined above. Notable blood pressure findings will be hypertension (systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg) or hypotension (systolic blood pressure of < 90 mmHg and/or a diastolic blood pressure of < 60 mmHg). A blood pressure indicative of prehypertension (systolic blood pressure of 120 to < 140 mmHg and/or diastolic blood pressure of 80 to < 90 mmHg) will not be regarded as notable. A normal pulse rate will be defined as a rate of 60 to 100 beats per minute (bpm) under the measurement conditions outlined above. Notable pulse rate will be a rate below 60 bpm (bradycardia) or above 100 bpm (tachycardia). Whether action needs to be taken to address notable vital signs will be decided by the Investigator, taking into account the overall status of the participant. No specific action is foreseen as part of the study protocol.

8.4.1 Laboratory evaluations

A central laboratory will be used for the efficacy analysis of NT-proBNP (at randomization and Week 12 visit). No reconciliation with the central laboratory will be done for the local NT-proBNP used during the screening epoch. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to Investigators in the laboratory manual.

For the remaining laboratory evaluations only local laboratory will be used. Laboratory values will not be entered in eCRF (except NT-proBNP from screening).

Clinically notable laboratory findings are defined in Appendix 1.

Complete safety laboratory evaluations (Table 8-3) will be performed in the fasting state at the times indicated in Table 8-1.

Study procedures may be performed without restriction while the local laboratory results are pending. In these cases, the Investigator or designee should review the local laboratory results

as soon as they become available to decide whether any adjustments in the participant's study drug or non-study drug regimen are needed.

The Investigator must assess laboratory values that exceed the boundaries of notable laboratory abnormality and perform additional laboratory evaluations as judged appropriate. If the laboratory abnormality is the primary reason for an unforeseen hospitalization or otherwise fulfills the seriousness category of an AE, then the procedure for rapid notification of SAEs must be followed. Likewise, if the laboratory abnormality leads to discontinuation from the study drug (temporarily or permanently), the participant must be followed until the abnormality resolves or until it is considered permanent. The investigation may include continued monitoring by repeat laboratory testing or by additional laboratory tests as deemed necessary by the Investigator or the ARO/Novartis medical monitor.

Table 8-3 Laboratory assessments

Test category	Test name
Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be quantified.
Chemistry	Blood urea nitrogen, glucose, creatinine, total bilirubin, aspartate, aminotransferase, alanine aminotransferase, alkaline phosphatase, sodium, potassium, and chloride will be measured.
Additional tests	Blood samples will be obtained at the times indicated in Table 8-1 to determine changes in NT-proBNP (details will be provided in the laboratory manual).
Pregnancy test	All female participants of childbearing potential will have a serum pregnancy test performed at Visit 1. Additionally, these participants will have urine pregnancy tests performed at the times indicated in Table 8-1. In case of a positive urine pregnancy result, a confirmatory serum pregnancy test will be performed at the local laboratory.

8.4.2 Electrocardiogram

A standard 12-lead ECG will be performed at Screening (Visit 1), and at the times indicated in Table 8-1. Interpretation of the tracing must be made by a qualified physician and documented on the Electrocardiogram eCRF page. Each ECG tracing should be kept in the source documents at the study site labeled with study number, participant initials, participant number, and date. Any identifier details (e.g., participant initials, date of birth) must be redacted from all ECGs.

Only clinically significant abnormalities should be reported on the Electrocardiogram eCRF page. Clinically significant abnormalities should also be recorded on the relevant Medical History/Current Medical Conditions or Adverse Events eCRF page.

For any ECGs with participant safety concerns, 2 additional ECGs must be performed to confirm the safety finding. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at Randomization before administration of study treatment.

In the event that a clinically significant ECG abnormality is identified at the study site (e.g., severe arrhythmia, conduction abnormality, or QTcF > 500 ms), a copy of the assessment is to be sent to the local laboratory for expedited review if applicable, and the ECG is repeated to

confirm the diagnosis. If the participant 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 AEs as appropriate.

8.4.3 Pregnancy and assessments of fertility

All female participants of childbearing potential will have a serum pregnancy test performed at Visit 1 and EOS along with monthly urine pregnancy tests. In case of a positive urine pregnancy result, a confirmatory serum pregnancy test will be performed at the local laboratory. See Section 10.1.4 for details on pregnancies.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of childbearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile

In the absence of the above medical documentation, follicle-stimulating hormone testing is required of any female participant, regardless of reported reproductive/menopausal status at Screening/Randomization.

8.4.4 Other safety evaluations

8.4.4.1 Adverse events of special interest

8.4.4.1.1 Angioedema

Angioedema is a type of abrupt swelling that occurs under the skin and/or mucous membranes and is often localized to the head, neck, throat, and/or tongue, but may occur elsewhere, including the genitalia and intestines. Severe cases may be associated with airway compromise. Although, the mechanism is not fully understood, bradykinin has been implicated as the putative mediator. Therefore, medications that raise the levels of endogenous bradykinin by inhibiting the enzymes responsible for its breakdown, such as ACE, aminopeptidase P, and NEP, may result in this potentially dangerous side effect.

Simultaneous inhibition of multiple breakdown pathways of bradykinin is thought to significantly increase the risk of occurrence of angioedema (Sulpizio et al 2004). Section 4.1 details how to avoid the simultaneous inhibition of the ACE and NEP pathways at Visit 101 (Randomization). The method outlined in Section 4.1 is expected to provide at least 36 hours free of significant simultaneous inhibition of NEP and ACE, thereby minimizing the potential risk of occurrence of angioedema. This 36-hour washout is expected to present minimal risk to participants, especially since all participants will continue using their other background HF medications during this period.

8.4.4.1.2 Other adverse events of special interest

Other AEs of special interest that will be collected are arrhythmias, symptomatic hypotension, hyperkalemia, and renal dysfunction.

8.4.5 Appropriateness of safety measurements

Participants subjected to treatment with ACEIs or NEP inhibitors are at increased risk of angioedema, which warrant special safety measurements.

The remaining safety assessments are standard for this indication and participant population.

8.5 Additional assessments

8.5.1 Biomarkers

NT-proBNP will be measured in all participants in the Main Study at Randomization and Week 12 as a component of the primary endpoint.

In addition, for participants who consent to participate in the biomarker additional assessment, changes from Randomization to Week 6 and Month 8 will be analyzed for blood biomarkers related to CV function/injury, fibrosis, and remodeling, aiming to elucidate if biomarkers are associated with event risk or disease progression as well as the effect of the study drugs on these markers. It is estimated that a subset of approximately ~550 participants will be included in the biomarker analysis.

Biomarkers that will be measured may include, but are not limited to:

1. markers of myocardial remodeling: e.g. MMP-2, MMP-9, TIMP-1, PINP, and PIIINP
2. markers of myocardial fibrosis and injury: e.g. high-sensitivity troponin T (hsTnT), aldosterone, and sST2
3. markers of myocardial stress: e.g natriuretic peptides
4. *Trypanossoma cruzi* parasitemia and serology will also be measured in order to explore its association with clinical endpoints. Furthermore, the association of this parasitological biomarker with other biomarkers signatures will be explored

The analysis of circulating markers is also planned to examine the effect of sacubitril/valsartan on protein expression and may support the identification of biomarker signatures that characterize CCC disease progression and the response to treatment with sacubitril/valsartan.

In addition, the comparison with other patients cohorts are also planned (patients with HFrEF without CCC and patients with Chagas disease but without HFrEF) aiming to gain insights into CCC pathophysiology.

Instructions for sample collection, numbering, processing, and shipment will be provided in the laboratory manual.

DNA sampling/pharmacogenetics

The study also includes an optional genetic research component which requires a separate informed consent signature if the participants agree to it. As permitted by local governing regulations and by IRBs/IECs, it is required as part of this protocol that the Investigator presents this option to the participant.

The purpose of genetic research is to determine biomarker signatures in order to gain insight into the molecular mechanisms that underlie CCC development (by comparing with other patient cohorts [patients with HFrEF without CCC and patients with Chagas disease but without HFrEF]) and treatment response. As technology changes over time, the most appropriate technology will be used at the time the exploratory genetic research is performed. This may include high density SNP array or the study of the entire genome.

DNA samples

The use of DNA to search for biomarkers of disease and drug action is exploratory. Any results from this DNA study will not be placed in the participant's medical records.

To maximize confidentiality, all samples and the information associated with the samples will be double-coded to prevent the exposure of the participant's information and identity. This double-coding process allows Novartis to go back and destroy the sample at the participant's request. In addition, sample information is stored in a secured database while genetic data is stored in an independent secured database.

8.5.2 Holter monitoring

The pathophysiology of CCC leads to ventricular arrhythmias which have been associated with high rates of morbidity and mortality (Barbosa et al 2015, Ribeiro et al 2012).

In PARADIGM-HF, sacubitril/valsartan reduced the risk of resuscitated and non-resuscitated sudden death by 22% compared with enalapril (Desai et al 2015). In addition, in a study with 120 HFrEF patients with ICD, sacubitril/valsartan decreased ventricular arrhythmias and ICD shocks compared with ramipril or valsartan (de Diego et al 2018).

Therefore, considering the arrhythmia burden in participants with CCC and the potential antiarrhythmic effects of sacubitril/valsartan, Holter monitoring will be performed at Randomization and at Month 8 in a subset of approximately 400 participants.

Additional details of the Holter monitoring assessment are outlined in Appendix 6.

8.5.3 Magnetic resonance imaging

Myocardial delayed enhancement by MRI quantifies myocardial fibrosis in patients with CCC, which increases progressively according to the severity of the disease (Rochitte et al 2005)

Also, myocardial fibrosis seems to be an independent predictor of adverse long-term outcome in CCC, supporting the use of cardiac MRI in better risk-stratifying this population and possibly guiding therapy (Senra et al 2018, Volpe et al 2018).

Therefore, in order to gain a better understanding of the potential impact of sacubitril/valsartan on cardiac structure, function, and fibrosis, MRI will be performed at Randomization and at

Month 8 in a subset of approximately 100 participants (approximately 50 from each treatment group) at selected study sites. Additional details of the MRI additional assessment are outlined in Appendix 7.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to planned duration), and can be initiated by either the participant or the Investigator.

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

Study treatment must be discontinued under the following circumstances:

- participant decision
- pregnancy
- use of prohibited treatment as per recommendations in the prohibited treatment section
- any situation in which study participation might result in a safety risk to the participant
- any laboratory abnormalities that in the judgment of the Investigator, taking into consideration the participant's overall status, prevents the participant 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 participant's premature discontinuation of study treatment and record this information.

Participants 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, e-mail, or letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

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

After study treatment discontinuation, 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/SAEs

The Investigator must also contact the IWRS to register the participant's discontinuation from **study treatment**.

9.1.2 Withdrawal of informed consent

- Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant:does not want to participate in the study anymore, and
- does not allow further collection of personal data

In this situation, the Investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw his/her consent and record this information.

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 participant are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the participant's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a participant's samples until their time of withdrawal) according to applicable law.

All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

Participants who withdraw their consent to participate in the additional assessments will still be able to participate in the Main Study provided they keep their consent to this part.

9.1.3 Lost to follow up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g., dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the Sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible (provide instruction for contacting the participant, when the participant should stop taking drug, when the participant should come for a final visit) and treated as a prematurely withdrawn participant. 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 participant's interests. The Investigator or ARO depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the study.

9.2 Study completion and post-study treatment

The study will be completed when reaching 302 CV events **or** if a recommendation is made by the DMC to prematurely stop the study. At the end of the study, all participants will return for the final end of study (EOS) visit (Visit 199) and be asked to return the remaining study drug.

The Investigator must provide follow-up medical care for all participants who complete the study and all participants who are prematurely withdrawn from study drug, or must refer them for appropriate ongoing care. This care may include continuation of treatment with commercialized available sacubitril/valsartan treatment or switching participants to ACEI/ARBs in addition to other guidelines recommended HF medications, according to the Investigators judgment. Due to the potential risk of angioedema when sacubitril/valsartan used concomitantly with an ACEI, ACEI therapy must not be restarted until 36 hours after discontinuing of sacubitril/valsartan.

Study completion is defined as when the last participant finishes their End-of-study 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 participant will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them).

All randomized and/or treated participants should have a safety follow-up call conducted 30 days after the EOS. The information collected is kept as source documentation. All SAEs reported during this period must be reported as described in Section 10.1.3. Attempts to contact the participant should be recorded in the source documentation.

10 Safety monitoring and reporting

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 participant or 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.

Medical personnel qualified by ARO will be readily available to advice on study-related medical questions or problems.

The occurrence of AEs must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the

participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

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 underlying disease. Investigators have the responsibility for managing the safety of individual participant and identifying AEs. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded in the Adverse Events eCRF 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. 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. relationship to the study treatment
3. duration (start and end dates)
4. whether it constitutes a SAE and which seriousness criteria have been met
5. action taken 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/withdrawn

6. outcome, i.e., its recovery status or whether it was fatal. If the event is ongoing, an outcome of not recovered/not resolved must be reported

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

Adverse events (including laboratory 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.

Information about adverse drug reactions for the investigational drug can be found in the IB. Any new information regarding the safety profile of the medicinal product that is identified between IB 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 has then to be discussed with the participant.

10.1.2 Serious adverse events

An SAE is defined as any AE (appearance of or worsening of any pre-existing one) undesirable sign, symptom, or medical conditions 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 participant is at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D guidelines).

- 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 participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a 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 participant 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 ER or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

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 SAEs irrespective if a clinical event has occurred.

10.1.3 Serious adverse event reporting

To ensure the safety of participants, every SAE (excluding the study endpoints), regardless of causality, occurring after the participant has provided informed consent and either until the time the participant is deemed a screen failure or until 30 days following the last administration of study treatment must be reported to ARO/Novartis Safety within 24 hours of learning of its occurrence.

Information about all SAEs is collected and recorded on the (electronic) Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The Investigator must assess the relationship of each SAE to each specific component of study treatment, (if study treatment consists of several components) complete the SAE Report Form in English, and submit the completed form within 24 hours to the ARO/Novartis Safety. Detailed instructions regarding the submission process and requirements for signature are to be found in the Investigator folder provided to each study site.

The following pre-defined study endpoints are excluded from the expedited reporting of AEs and SAEs:

- CV death
- HF hospitalization
- all-cause mortality
- sudden death or resuscitated sudden cardiac arrest
- ER visits due to HF (where intravenous therapy is required)

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 of 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 IB or Package Insert (new occurrence) and is thought to be related to the study treatment, an associate from Patient Safety Department 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.

Suspected unexpected serious adverse reactions (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 participating countries.

10.1.3.1 Special reporting requirements

In outcome studies, some of the efficacy endpoints potentially meet the requirements for SUSAR reporting. The regulations have allowed an exemption from expediting safety notifications from SUSAR cases, aimed at ensuring the validity of an outcome study (European Commission ENTR/CT13 Guideline 2006, Chapter 5.1.9. Managing adverse reactions/events in trials with high morbidity and high mortality diseases and where efficacy end-points could also be SUSARs; FDA Guidance 2012).

Therefore, Novartis will NOT expedite a report to competent authorities/relevant ECs and will NOT issue an IN for disease related endpoints and AEs commonly seen in study population, as described below. These events will be presented in the clinical study report at the end of the study.

- pre-specified disease-related endpoints
- cardiovascular death, HF hospitalization, sudden cardiac death, arrhythmogenic cardiomyopathy
- adverse events that are commonly seen in the study population with HF
  - in clinical studies evaluating treatments for high morbidity and/or high mortality disease states, Investigators may report AEs or SAEs that are commonly seen in the study population (Table 10-1). SAEs that are not study endpoints, such as known consequences of the underlying disease or condition under investigation, or events common in the study population, are anticipated to occur with some frequency during the course of the study, regardless of drug exposure

Table 10-1 Adverse events that are commonly seen in the study population (Chagas cardiomyopathy)

CV events		Non CV events	
Unstable angina	Generalized edema	Arthralgia/arthritis	COPD (including bronchitis and emphysema)
Arrhythmia	Hypertension	Constipation	Cough
Transient ischemic attack	Hypotension	Diarrhea	Fatigue
Renal impairment	Peripheral edema	Headache	Sepsis
Chest pain	Syncope	Nausea	Nasopharyngitis
Dizziness/vertigo	Angina pectoris	Anemia	Pneumonia
Cerebrovascular accident	Dyspnea	Upper respiratory infection/insufficiency	Dementia

An external independent Data Monitoring Committee (DMC) (see Section 10.2.2) will be appointed and will review efficacy and safety data of the ongoing study on a regular basis. The opinion and recommendations from the DMC will be notified by Novartis as soon as possible to the competent authorities and the ECs where they qualify for expedited reporting.

If specifically requested by a local Health Authority, pre-specified endpoints (see above) that also meet the criteria for SUSARs will be expedited to this Health Authority. Investigator Notifications will not be issued for these events.

Any other SUSAR that does not meet the pre-specified disease-related endpoints as mentioned above will be reported to competent authorities and relevant ethics committees and issuance of an IN will occur.

Any SAEs experienced after the 30-day period following the last administration of study treatment should only be reported to ARO/Novartis Safety if the Investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to ARO/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 and reported by the Investigator to the ARO/Novartis Safety Department. Pregnancy follow up should be recorded on the same form and should include an assessment of the possible relationship to study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 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, participant, or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately not used 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 eCRF whether or not associated with an AE/SAE and reported to ARO/Novartis Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database as SAEs within 24 hours of Investigator's awareness (Table 10-2).

Table 10-2 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in dosing eCRF (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 an SAE

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

10.2 Additional safety monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring, and evaluation of liver events has to be followed.

The following 2 categories of abnormalities/AEs have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate eCRFs

Please refer to Table 16-1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-1 should be followed up by the Investigator or designated personnel at the study site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2. Repeat liver chemistry tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin [TBL], prothrombin time/international normalized ratio [PT/INR], alkaline phosphatase [ALP], and gamma-glutamyl transferase [GGT]) to confirm elevation.

- these liver chemistry repeats should be performed using the local laboratory used by the study site. Repeated laboratory test results must be reported as appropriate
- if the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate
- discontinuation of the investigational drug (refer to Section 9.1.1), if appropriate
- hospitalization of the participant if appropriate
- causality assessment of the liver event
- thorough follow up of the liver event should include:
    - These investigations can include based on Investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and the procedures performed must be recorded as appropriate in the eCRF.

10.2.2 Data Monitoring Committee

This study will include a DMC, which will function independently of all other individuals associated with its conduct, including the study site Investigators. The DMC will assess at defined intervals the progress of the clinical study, safety data, and critical efficacy variables and recommend to the Sponsor whether to continue, modify, or terminate a study.

Specific details regarding composition, responsibilities, data monitoring and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the Sponsor/ARO and the DMC.

10.2.3 Adjudication Committee

The primary endpoint will be confirmed by an independent Clinical Endpoint Adjudication Committee.

The role of the Clinical Endpoint Adjudication Committee is to ensure that all treatment outcomes are judged uniformly, using standard criteria and processes. The Clinical Endpoint Adjudication Committee will be led by the Brazilian Clinical Research Institute and composed of clinical experts to evaluate disease progression and harmonize endpoint assessment criteria using predefined endpoint definitions.

All personnel involved in the adjudication process will remain blinded to treatment allocation throughout the study. Specific details regarding endpoint definitions can be found in the Clinical Endpoints Adjudication Committee Manual of Operations.

11 Data collection and database management

11.1 Data collection

Designated Investigator staff will enter the data required by the protocol into the eCRFs, which have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, study site staff will not be given access to the 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 recorded on eCRFs 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 participant data for archiving at the study 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

The ARO personnel 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 study site via the EDC system. Designated study site staff is 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 WHO Drug Reference List (Version B2 or later), which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be

coded using the medical dictionary for regulatory activities (MedDRA version 22.0 or later) terminology.

Randomization codes and data about all study treatments dispensed to the participant and all dosage changes will be tracked using the IWRS. The system will be supplied by the ARO, who will also manage the database. The data will be sent electronically to Novartis (or a designated Country Research Organization) at specific timelines.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Study site monitoring

Before study initiation, at a study site initiation visit or at an Investigator's meeting, an ARO representative(s)/Novartis will review the protocol and data capture requirements (i.e., eCRFs) with the Investigators and their staff. During the study, several methods of ensuring protocol and GCP compliance and the quality/integrity of the study sites' data will be used. The field monitor will visit the study site to check the completeness of participant 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 study site's data may be performed by the ARO/Novartis/delegated Country Research Organization/Country Research Agency. Additionally, a central analytics organization may analyze data & identify risks & trends for study site operational parameters, and provide reports to ARO/Novartis clinical teams to assist with study oversight.

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, ECGs, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the participant's file. The Investigator must also keep the original model informed consent form signed by the participant (a signed copy is given to the participant).

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 participants will be disclosed.

12 Data analysis and statistical methods

The analysis will be conducted on all participant data at the time the study ends. Additional details of the statistical analyses will be documented in a statistical analysis plan.

12.1 Analysis sets

The Randomized Analysis Set (RAN) consists of all randomized participants.

The Full Analysis Set (FAS) comprises all participants to whom study treatment has been assigned by randomization. According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to during the randomization procedure.

The Safety Set (SAF) includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

The Per-Protocol Set (PPS) is a subset of participants of the FAS and will include participants with no major protocol deviations. The PPS will be used to support the primary efficacy analysis.

12.2 Demographics and other baseline characteristics

Baseline value is the last non-missing assessment before the first administration of study drug, unless specified otherwise.

Summary statistics will be provided by treatment arm for demographics and baseline characteristics, including age, age group, sex, race, ethnicity, weight, height, body mass index (BMI), category of prior HF medication, prior HF hospitalization, NYHA class, NT-proBNP, and vital signs (blood pressure and pulse rate). Body mass index will be calculated as weight (Kg)/height^2 (m^2) from the collected height and weight at the Screening visit. Continuous variables will be summarized using n, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency and percentage. Additionally, summary statistics will be provided by treatment and age group.

The FAS will be the participant population for the above analyses.

12.3 Treatments

The overall duration on study drug will be summarized by treatment group using mean, standard deviation, median, minimum, and maximum. Additionally, the number and percentage of participants will be summarized by treatment group for duration category. Concomitant medications and significant non-drug therapies, prior to and after the randomization date respectively, will be summarized by therapeutic class, preferred term, and treatment group for the safety population. The number and percentage of participants on different HFrEF background medications (e.g., aldosterone antagonists, β-blockers, diuretics, digoxin) will be tabulated by treatment at Baseline and during the double-blind stage.

The SAF will be used for the above analyses.

12.4 Analysis of the primary endpoint

12.4.1 Definition of primary endpoint

The primary endpoint is the hierarchically ordered composite consisting of time to CV death (worst category; earlier time to CV death is unfavorable), time to first HF hospitalization (second worst category; earlier time to HF hospitalization is unfavorable), and the relative change from Baseline to Week 12 in NT-proBNP levels (best category; more reduction or less increase are favorable) (Table 2-1). CV events will be confirmed by an independent Endpoint Adjudication Committee.

The effect is measured through the unmatched win ratio. The win ratio is based on pair-wise comparisons between participants receiving sacubitril/valsartan and participants receiving enalapril. A winner in the pair-wise comparison has a delayed time to the occurrence of CV death; if time to the occurrence of CV death is censored, a winner has a delayed time to the occurrence of first HF hospitalization event; if the times to both CV events are censored, a winner has a smaller change in NT-proBNP between Baseline and Week 12.

12.4.2 Statistical model, hypothesis, and method of analysis

The following primary analysis will be tested (Wang and Pocock 2016):

H_0: $\Psi \leq 1$ (win ratio ≤ 1). The true number of 'winners' for sacubitril/valsartan is less than or equal to the true number of winners for enalapril.

H_1: $\Psi > 1$ (win ratio > 1). The true number of 'winners' for sacubitril/valsartan is larger than the true number of winners for enalapril.

The primary efficacy endpoint will be analyzed using the win ratio approach (Pocock et al 2012), with treatment as fixed-effect factor and stratified by country (Dong et al. 2017). Every participant in the sacubitril/valsartan arm will be compared to every participant in the enalapril arm within each stratum (country). All pairs will be compared first by time to CV death; if there is no winner, they will be compared for time to first HF hospitalization; if again there is no winner, they will be compared according to reduction in NT-proBNP levels between randomization and Week 12. If the comparison between changes in NT-proBNP levels does not result in a winner, the respective pairwise comparison is tied. When comparing the time to an event between two participants and at least one of the times is censored, the comparison is only performed up to the censoring time. The comparison of NT-proBNP is performed based on the relative change between randomization and Week 12 and takes into account that relative changes within $\pm 25\%$ are considered medically irrelevant; in detail, let x_{LCZ696} and x_{Enal} be the relative changes of participants in the sacubitril/valsartan and the enalapril arm, respectively.

Then, a comparison of NT-proBNP is in favor of the participant in the sacubitril/valsartan arm if $x_{LCZ696} < 0.75\, x_{Enal}$. On the other hand, the comparison is in favor of the participant in the enalapril arm if $x_{Enal} < 0.75\, x_{LCZ696}$.

The win ratio is estimated by the ratio of the number of winners in the sacubitril/valsartan group and the number of winners in the enalapril group with weights defined as the reciprocal of the stratum (country) sample size.

$$\Psi = \frac{\sum_{m=1}^{M} w^{(m)} n_{LCZ696}^{(m)}}{\sum_{m=1}^{M} w^{(m)} n_{Enal}^{(m)}}$$

Where $n_{LCZ696}^{(m)}$ and $n_{Enal}^{(m)}$ are the total number of wins in the mth stratum for the sacubitril/valsartan and Enalapril groups, respectively; $w^{(m)} = {}^{1}/_{N^{(m)}}$ and N$^{(m)}$ is the total sample size in the mth stratum.

The estimated win ratio and the corresponding 2-sided 95% CI will be provided. The FAS will be used for the primary analysis.

The overall Type I error rate will be controlled at 2.5% (1-sided).

The contribution to the number of winners of each component of the win ratio will be reported.

The number and percentage of CV events breaking down by event type will be summarized. NT-proBNP at each visit and change from Baseline will be summarized. The summary will be presented by treatment group for both the FAS and the PPS.

12.4.3 Handling of missing values/censoring/discontinuations

12.4.3.1 Time to CV death

The time from randomization to CV death will be considered as censored at the final analysis for participants who have not experienced a CV death and for whom at least one of the following applies at or prior to the analysis time point:

- withdrawal of informed consent
- loss to follow up
- death from non-CV causes

The censoring date for those participants without CV death prior to the analysis time point will be whichever occurs first of the following:

- date of withdrawal of informed consent
- date of last visit (Visit 199)
- date of death from non-CV causes

12.4.3.2 Time to first HF hospitalization

The time from randomization to first HF hospitalization will be considered as censored at the final analysis for participants who have not experienced a HF hospitalization and for whom at least one of the following applies at or prior to the analysis time point:

- withdrawal of informed consent
- loss to follow up
- cardiovascular death
- death from non-CV causes

The censoring date for those participants without a HF hospitalization prior to the analysis time point will be whichever occurs first of the following:

- date of withdrawal of informed consent
- date of last visit (Visit 199)
- date of death from CV cause
- date of death from non-CV causes

12.4.3.3 NT-proBNP measurement at Week 12

Cardiovascular death and HF hospitalization are at a higher hierarchy level than NT-proBNP in the composite primary endpoint for win ratio analysis. Therefore, missing values due to CV death or after HF hospitalization do not affect the analysis. Missing NT-proBNP measurements at Week 12 due to other reasons (e.g., non-CV death) are expected to be infrequent; they may result in more ties with minimal impact on the power. Therefore, no imputation will be done for missing NT-proBNP measurement at Week 12 for primary analysis.

12.4.4 Sensitivity and supportive analyses

Supportive analyses

In addition to the primary analysis, the primary efficacy endpoint will be supportively analyzed for the PPS by means of the same primary analysis model.

Additional analyses will be performed on each individual component of the primary endpoint that occurs during the Randomized Treatment Epoch of the study to quantify the strength of the effect of each component.

For CV death and first HF hospitalization:

- Cox's proportional hazard model will be used to analyze time to CV death, and time to first HF hospitalization, respectively, with treatment as fixed-effect factor and stratified by country
- a log-rank test will be performed for both the FAS and the PPS
- the survival function for each treatment arm will be estimated by the Kaplan-Meier method presenting curves for each treatment arm for both the FAS and the PPS

For NT-proBNP:

An ANCOVA model will be used to analyze the change of NT-proBNP from Baseline to Week 12, with treatment and country as fixed-effect factors and baseline NT-proBNP as covariate.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy endpoints

The secondary efficacy endpoints are:

1. time from randomization to first composite CV event
2. time from randomization to all-cause mortality
3. time from randomization to sudden death or resuscitated sudden cardiac arrest
4. number of visits to an ER due to HF (where intravenous therapy is required)
5. number of days alive out of the hospital

12.5.1.1 Analysis of the time to the occurrence of the composite CV outcome

The time from randomization to the occurrence of the composite of CV death or first HF hospitalization will be analyzed using Cox's proportional hazards model with treatment and country as fixed-effect factors. The estimated hazards ratio and the corresponding 2-sided CI will be provided for the FAS.

The Kaplan-Meier curves by treatment arm will be presented for the FAS. Additionally, the frequency and percentage of participants with a composite CV event will be provided by treatment arm.

12.5.1.2 Analysis of the time to all-cause mortality

The time from randomization to all-cause mortality will be analyzed using Cox's proportional hazards model with treatment and country as fixed-effect factors. The estimated hazards ratio and the corresponding 2-sided CI will be provided for the FAS.

The Kaplan-Meier curves by treatment arm will be presented for the FAS. Additionally, the frequency and percentage of all-cause mortality will be provided by treatment arm.

12.5.1.3 Analysis of the time to sudden death or resuscitated sudden cardiac arrest

The time from randomization to sudden death or resuscitated sudden cardiac arrest will be analyzed using Cox's proportional hazards model with treatment and country as fixed-effect factors. The estimated hazards ratio and the corresponding 2-sided CI will be provided for the FAS.

The Kaplan-Meier curves by treatment arm will be presented for the FAS. Additionally, the frequency and percentage of sudden deaths or resuscitated sudden cardiac arrests will be provided by treatment arm.

12.5.1.4 Analysis of the number of visits to an ER due to HF

The rate of visits to an ER due to HF (where intravenous therapy is required) will be analyzed using a generalized linear model assuming a negative binomial distribution. The time at risk for a participant is the length of follow-up. The analysis model will include terms for treatment and

country. An estimate of the ratio of event rates between the treatment arms, together with the 95% CI, will be presented for the FAS.

The number of visits to an ER due to HF (where intravenous therapy is required) during the treatment period will be summarized by treatment arms, as continuous variables and as categorical variables classified into 0, 1, 2, 3, ≥ 4 events.

12.5.1.5 Analysis of the number of days alive out of the hospital

The duration in days of hospital-free survival will be summarized by treatment group, and descriptive statistics (n, mean, standard deviation, median, max, and min) will be provided. The mean difference between treatment groups will be compared using ANCOVA model with treatment and follow-up time. The estimated within treatment means, between-treatment different and 95% CI will be provided for FAS.

12.5.2 Safety endpoints

The safety and tolerability assessments are:

a. physical examination
b. vital signs (sitting systolic and diastolic blood pressure, and pulse)
c. laboratory evaluations
d. pregnancy assessment
e. electrocardiogram
f. adverse events
g. serious adverse events
h. adverse events of special interest:
    - arrhythmia
    - angioedema
    - symptomatic hypotension
    - hyperkalemia
    - renal dysfunction

For all safety analyses, the Safety Set will be used. All listings and tables will be presented by treatment arm.

Safety summaries (tables, 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).

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

Vital signs

All vital signs data will be listed by treatment arm, participant, and visit/time and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Twelve-lead ECG

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

Adverse events

All information obtained on AEs will be displayed by treatment arm and listed by participant.

The number (and percentage) of participants with treatment emergent AEs (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 in the following ways:

- by treatment, primary system organ class and preferred term
- by treatment, primary system organ class, preferred term and maximum severity

Separate summaries will be provided for study medication-related AEs, death, SAEs, other significant AEs leading to discontinuation.

A participant with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

Adverse events of special interest

The number (and proportion) of participants with AEs of special interest (i.e., angioedema, symptomatic hypotension, hyperkalemia, and renal dysfunction) will be summarized by treatment.

Resource utilization

Data relating to resource utilization will be used for the purpose of economic evaluation and will be carried out and reported as a separate activity.

12.6 Analysis of exploratory endpoints

The exploratory endpoints are:

1. Number of ventricular fibrillation or sustained ventricular tachycardia needing specific pharmacological, electrical, or other treatment
2. Number of anti-tachycardia pacing or shock therapies (in the subset of participants with an ICD or CRT-D at Randomization)

Exploratory analyses will be performed on the FAS unless specified otherwise. There will be no formal inferential analyses.

Descriptive summary statistics over time for baseline, actual value, and change from Baseline will be presented for each treatment arm.

The number of sustained ventricular tachycardia events needing specific treatment or ICD implantation will be analyzed using a negative binomial model (McCullagh and Nelder 1989) with the count data as the dependent variable and treatment group and country as fixed-effect factors and log(follow-up duration) as the off-set. The model estimated event rates (intensities/risk rate) and their 95% CIs will be provided by treatment group. The treatment comparison will be performed through the estimated ratio of risk rates. The estimated reduction in risk rate and its 95% CI will also be provided. Note that, in case when the follow-up durations depend on the treatments (informative censorings), the estimated rate reduction should be interpreted with caution. However, when sacubitril/valsartan has a reduction in mortality, the rate reduction estimated from the negative binomial model will become conservative.

The results from the additional assessments (Holter monitoring and MRI) will be reported separately from the CSR according to the analyses plans in Appendix 6 and Appendix 7.

Biomarkers

NT-proBNP will be collected for all patients. Additional biomarkers will be collected for a subset of patients who consent to participate.

Absolute values and change from baseline values will be summarized descriptively by treatment group and visit. The geometric mean will be included in the summary tables as well as the standard summary statistics. Change in log-transformed ratio to baseline biomarkers will be analyzed using a Mixed Model of Repeated Measurements (MMRM), log-transformed baseline will be fitted in the model as a covariate. All results will be exponentiated prior to presentation.

Baseline is defined as assessment values taken at randomization. Biomarker analyses will be performed in the FAS and reported separately from the CSR.

12.7 Interim analyses

No interim efficacy analysis is planned.

Interim safety assessments are planned to be performed every 6 months by an independent statistician not involved in the study conduct. No alpha adjustment will be made. The results will be reviewed by the independent DMC.

To reduce bias, all study team members involved in data analysis will remain blinded to the treatment codes and the results of the interim analysis until all monitoring decisions are made and the database is locked for final analysis.

12.8 Sample size calculation

12.8.1 Primary endpoint

An analysis of the 55 participants with Chagas' disease in the enalapril group in PARADIGM-HF showed an event rate of 20 events per 100 participant-years for CV death plus hospitalization due to HF. Similar event rates, for CV death plus hospitalization due to HF in CCC participants, has also been seen in the BENEFIT (Morillo et al 2015) and SHIFT (Bocchi et al 2018) studies. Therefore, we assumed a rate of approximately 20 events per 100 participant-years for the CV event (composite of CV death and first HF hospitalization) for the enalapril group.

Approximately 66% of the first CV events are HF hospitalizations. For the sample size calculation, we assumed a rate of 16 events per 100 participant-years for the sacubitril/valsartan group, which corresponds to an effect of 20%.

The sample size was determined based on a simulation study under the assumptions of

- a 1-sided type I error rate of 2.5%
- a target power of 85%
- a uniform accrual of 18 months
- a study duration of 36 months, i.e. the individual follow-up times varied between 18 and 36 months
- an annualized event rate of 0.16 for the composite of CV death or first HF hospitalization in the sacubitril/valsartan group, and an annualized event rate of 0.20 for the composite of CV death or first HF hospitalization in the enalapril group
- a relative change of NT-proBNP between Week 12 and Baseline that is 25% lower in the sacubitril/valsartan group compared to the enalapril group

During the simulation study, a simulated study was considered to show superiority of sacubitril/valsartan over enalapril when the win ratio was significantly larger than one based on the 1-sided significance level of 2.5%, and the estimated hazard ratio of sacubitril/valsartan versus enalapril for time to first HF hospitalization was less than one, and the estimated hazard ratio of sacubitril/valsartan versus enalapril for CV death was less than one.

Based on these assumptions and criteria for superiority, a study with 900 participants results in the target power of 85%. Moreover, 302 participants with events for the composite of CV death or first HF hospitalization can be expected in the study.

As the primary hierarchical composite endpoint is evaluable as long as participants experience either a HF hospitalization, CV death, or have a NT-proBNP value measured at Week 12, the sample size calculation did not assume any loss to follow up.

A blinded sample size re-estimation may occur if the event rate is lower than expected or the number of participants lost to follow up is higher than expected during the study. A review will be done when 50% of participants have been enrolled. Otherwise, the study will continue until 302 participants have experienced a CV event and all participants have a minimum follow up of 12 weeks.

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 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 study, the Investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the study protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements), and any other written information to be provided to participants. 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 ARO monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the study site is requested by a regulatory authority, the Investigator must inform ARO 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 and as required in EudraCT. In addition, after study completion (e.g., defined as last participant last visit) and finalization of the study report the results of this study will be submitted for publication and posted in a publicly accessible database of clinical study results, such as the Novartis clinical study results website and all required Health Authority websites (e.g., clinicaltrials.gov, etc.).

Future sub-studies may be conducted to address other objectives and will be reported separately.

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 study 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 as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of study sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring, or performing quality control of the clinical study. 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 participants 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

ARO/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 participant 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, ARO/Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request

Andrade JP, Marin-Neto JA, Paola AA, et al (2011) I Latin American guidelines for the diagnosis and treatment of Chagas' cardiomyopathy. Arq Bras Cardiolog; 97 (2 suppl 3):1-48

Ayub-Ferreira SM, Mangini S, Issa VS, et al (2013) Mode of death on Chagas' heart disease: comparison with other etiologies. A subanalysis of the REMADHE prospective trial. PLoS Negl Trop Dis; 7 (4):e2176

Barbosa MP, Carmo AA, Rocha MO, et al (2015) Ventricular arrhythmias in Chagas disease. Rev Soc Bras Med Trop; 48(1):4-10

Bocchi EA (1994) Update on indications and results of the surgical treatment of heart failure. Arq Bras Cardiolog; 63 (6):523-30

Bocchi EA (2013) Heart Failure in South America. Curr Cardiol Rev; 9 (2):147-56

Bocchi EA, Marcondes-Braga FG, Bacal F, et al (2012) Updating of the Brazilian guideline for chronic heart failure. Arq Bras Cardiolog; 98 (1 suppl 1):1-33

Bocchi EA, Rassi S, Guimarães GV (2018) Safety profile and efficacy of ivabradine in heart failure due to Chagas heart disease: a *post hoc* analysis of the SHIFT trial. ESC Heart Fail; 5 (3):249-56

Botoni FA, Poole-Wilson PA, Ribeiro ALP, et al (2007) A randomised trial of carvedilol after renin-angiotensin system inhibition in chronic Chagas' cardiomyopathy. Am Heart J; 153 (6): 544-48

Brilla CG, Funck RC, Rupp H (2000) Lisinopril-mediated regression of myocardial fibrosis in patients with hypertensive heart disease. Circulation; 102(12):1388-93

de Diego C, Gonzalez-Torres L, Nunez JM, et al (2018) Effects of angiotensin-neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices.

Heart Rhythm; 15(3):395-02

Desai AS, McMurray JJ, Packer M, et al (2015) Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. Eur Heart J; 36:1990-97

Díez J, Querejeta R, López B, et al (2002) Losartan-dependent regression of myocardial fibrosis is associated with reduction of left ventricular chamber stiffness in hypertensive patients. Circulation; 105(21):2512-7

Dong G, Qiu J, Wang D, Vandemeulebroecke M (2017) The stratified win ratio. J of Biopharmaceutical Statistics; 28 (4): 778-96

Freitas HF, Chizzola PR, Paes AT, et al (2005) Risk stratification in a Brazilian hospital-based cohort of 1220 outpatients with heart failure: role of Chagas' heart disease. Int J Cardiol; 102 (2):239-47

Hansson L, Hedner T, Dahlöf B (1992) Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. Blood Press; 1(2):113-9

Izawa H, Murohara T, Nagata K, et al (2005) Mineralocorticoid receptor antagonism ameliorates left ventricular diastolic dysfunction and myocardial fibrosis in mildly symptomatic patients with idiopathic dilated cardiomyopathy: A Pilot Study. Circulation; 112(19):2940-45

McCullagh P, Nelder JA (1989) Generalized linear models, 2nd ed. London: Chapman and Hall

McMurray JJ, Packer M, Desai AS, et al (2014) PARADIGM-HF Investigators and committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med; 371 (11):993-1004

McMurray JJ, Packer M, Desai A, et al (2015) A putative placebo analysis of the effects of LCZ696 on clinical outcomes in heart failure. Eur Heart J; 36 (7):434-39

Morillo CA, Marin-Neto JA, Avezum A, et al (2015) Randomized trial of benznidazole for chronic Chagas' cardiomyopathy. N Engl J Med; 373(14):1295-306

Nunes MCP, Dones W, Morillo CA, et al (2013) Chagas' disease. An overview of clinical and epidemiological aspects. J Am Coll Cardiol; 62 (9):767-76

Nunes MCP, Beaton A, Acquatella H, et al (2018) Chagas Cardiomyopathy: An Update of Current Clinical Knowledge and Management: A Scientific Statement From the American Heart Association. Circulation; 138(12): e169-e209

Pocock SJ, Ariti CA, Collier TJ, et al (2012) The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J; 33(2):176-82

R Core Team (2020) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://.R-project.org/

Ramires FJA, Martinez F, Gómez EA, et al (2018) Post hoc analyses of SHIFT and PARADIGM-HF highlight the importance of chronic Chagas' cardiomyopathy. ESC Heart Fail; 5(6):1069-71

Rassi A Jr, Rassi A, Marin-Neto JA (2010) Chagas disease. Lancet; 375:1388–402

Ribeiro AL, Nunes MP, Teixeira MM, et al (2012) Diagnosis and management of Chagas disease and cardiomyopathy. Nat Rev Cardiol; 9:576-89

Rochitte CE, Oliveira PF, Andrade JM, et al (2005) Myocardial Delayed Enhancement by Magnetic Resonance Imaging in Patients With Chagas' Disease: A Marker of Disease Severity. J Am Coll Cardiol; 46(8):1553-58

Senra T, Ianni BM, Costa ACP, et al (2018) Long-Term Prognostic Value of Myocardial Fibrosis in Patients With Chagas Cardiomyopathy. J Am Coll Cardiol; 72(21):2577-87

Shen L, Ramires F, Martinez F, et al (2017) Contemporary characteristics and outcomes in chagasic heart failure compared with other nonischemic and ischemic cardiomyopathy. Circ Heart Fail; 10(11):e004361

SOLVD Investigators (1991) Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med; 325:293-302

SOLVD Investigators (1992) Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med; 327:685-91

Streefkerk H, Anand D, Zhou W, et a (2017) Safety of sacubitril/valsartan in patients receiving statins in the PARADIGM-HF trial. Heart Failure 2017 and 4th World Congress on Heart Failure organized by the Heart Failure Association of the ESC, 2017:159

Sulpizio AC, Pullen MA, Edwards RM, Brooks DP (2004) The effect of acute angiotensin-converting enzyme and neutral endopeptidase 24.11 inhibition on plasma extravasion in the rat. J Pharmacol Exp Ther; 309 (3):1141-47

Szajnbok FEK, Barretto ACP, Mady C, et al (1993) Beneficial effects of enalapril on the diastolic ventricular function in Chagas' cardiomyopathy. Arq Bras Cardiolog; 60 (4):273-78

Traina MI, Sanchez DR, Hernandez S, et al (2015) Prevalence and Impact of Chagas Disease Among Latin American Immigrants With Nonischemic Cardiomyopathy in Los Angeles, California. Circ Heart Fail; 8(5):938-43

Volpe GJ, Moreira HT, Trad HS, et al (2018) Left ventricular scar and prognosis in chronic Chagas cardiomyopathy. J Am Coll Cardiol; 72(21):2567-76

Wang D, Pocock S (2016) A win ratio approach to comparing continuous non-normal outcomes in clinical trials. Pharm stats; 15(3): 238-45

World health organization (2015) Chagas disease in Latin America: an epidemiological update based on 2010 estimates. Wkly Epidemiol Rec; 90: 33–43

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests. Notable values for blood pressure and pulse are presented in Table 8-2.

Liver function and related variables

Total bilirubin: > 2 x ULN

Alkaline phosphatase: > 2.5 x ULN

Renal function and electrolyte variables

Creatinine (serum): > 1.5 x ULN

Potassium: > 6 mmol/L or < 3 mmol/L

Sodium: > 160 mmol/L or < 115 mmol/L

Hematology variables

Red blood cell count > 50% increase, > 20% decrease

Hemoglobin > 50% increase, > 20% decrease

Hematocrit > 50% increase, > 20% decrease

White blood cell count > 50% increase, > 50% decrease

Platelet count > 75% increase, > 50% decrease

Clinical chemistry

Blood urea nitrogen > 50% increase

Creatinine > 50% increase

Creatine phosphokinase > 300% increase

Sodium > 5% decrease

Potassium > 20% increase, > 20% decrease

Chloride > 10% increase, > 10% decrease

Calcium > 10% increase, > 10% decrease

Uric acid > 50% increase

16.2 Appendix 2: Liver event and laboratory trigger definitions and follow-up requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/threshold
Liver laboratory triggers	• 3 x ULN < ALT/AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
Liver events	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any AE potentially indicative of a liver toxicity*
*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal	

Table 16-2 Follow up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case [a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record liver events to the appropriate eCRF page	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution [c] (frequency at Investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record liver events to the appropriate eCRF page	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution [c] (frequency at Investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record liver events to the appropriate eCRF page	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution [c] (frequency at Investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study treatment • Establish causality • Record liver events to the appropriate eCRF page	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution [c] (frequency at Investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms [b]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record liver events to the appropriate eCRF page	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution [c] (frequency at Investigator discretion)
> 3 to ≤ 5 × ULN (participant is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the participant	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Record liver events to the appropriate eCRF page	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record liver events to the appropriate eCRF page	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution [c] (frequency at Investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (participant is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the participant	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the participant • Establish causality • Record liver events to the appropriate eCRF page	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution [c] (frequency at Investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record liver events to the appropriate eCRF page	Investigator discretion

[a] Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

[b] (General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

[c] Resolution is defined as an outcome of one of the following: (1) return to Baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Based on Investigator's discretion investigation(s) for contributing factors for the liver event can include: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.3 Appendix 3: Specific renal alert criteria and actions and event follow up

Table 16-3 Specific renal alert criteria and actions

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50 % * **OR if <18 years old, eGFR ≤ 35 mL/min/1.73 m²**	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine **ratio** (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick	Assess & document • Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

* Corresponds to KDIGO criteria for Acute Kidney Injury

Table 16-4 Renal event follow up

FOLLOW-UP OF RENAL EVENTS

Assess, document and record in CRF

- Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells
- Blood pressure and body weight
- Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid
- Urine output

Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF

Monitor patient regularly (frequency at investigator's discretion) until -

- Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr) or
- Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.
- Analysis of urine markers in samples collected over the course of the DIN event

16.4 Appendix 4: Treatment guidelines for hyperkalemia (serum potassium greater than 5.3 mmol/L [mEq/L])

General principles

Elevation of serum* potassium levels above the predefined values should be repeated and confirmed before any action is taken.

Any participant with a serum* potassium > 5.3 mmol/L (mEq/L) at any time after randomization requires the Investigator to confirm the serum potassium concentration in a non-hemolyzed sample via an immediate repeat lab sample to the clinic local lab. Regular, repeated checks of serum potassium concentration (beyond that prescribed in the protocol) should continue until it is clear that the serum potassium concentration is stable and not rising into the range of concern (≥ 5.5 and < 6.0 mmol/L [mEq/L]*) or potential danger (≥ 6.0 mmol/L [mEq/L]*).

Participants with elevated serum potassium value will be managed according to the corrective actions outlined below. Hyperkalemia should be followed until resolution.

Corrective action for management of hyperkalemia

Serum potassium greater than 5.3 and less than or equal to 5.5 mmol/L (mEq/L) *

- confirm serum potassium concentration in a non-hemolyzed sample
- reinforce low potassium diet and restriction of food/drinks with high potassium content (e.g. orange juice, melon, bananas, tomatoes, dried fruits, potatoes, low-salt substitutes, tomatoes, coffee, etc.)
- correct metabolic acidosis if necessary.
- review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia. Consider reduction in dose or discontinuation of these agents:
    - potassium-sparing diuretics (e.g. amiloride and triamterene) including in combination products with thiazide or loop diuretics
    - potassium supplements, e.g. potassium chloride
    - salt substitutes
    - non-steroidal anti-inflammatory drugs (NSAIDs)
    - cyclo-oxygenase-2 (COX-2) inhibitors
    - trimethoprim and trimethoprim-containing combination products, such as Bactrim® and Septra® (trimethoprim/sulfamethoxazole fixed combination)
    - herbal supplements:

for example, noni juice, alfalfa (*Medicago sativa*), dandelion (*Taraxacum officinale*), horsetail (*Equisetum arvense*), nettle (*Urtica dioica*), milkweed, lily of the valley, Siberian ginseng, hawthorn berries

- assess participant for dehydration or any condition that could lead to dehydration (e.g. diarrhea, vomiting) and/or hypovolemia and initiate appropriate corrective measures of rehydration.

- repeat serum potassium measurement within 3 to 5 days
- if serum potassium remains > 5.3 and ≤ 5.5 mmol/L (mEq/L)*, regularly monitor serum potassium levels to ensure stability (suggested once monthly)
- consider down-titration of study drug, according to Investigator's medical judgment.

Serum potassium greater than 5.5 and less than 6.0 mmol/L (mEq/L)*

- confirm serum potassium concentration in a non-hemolyzed sample
- consider down-titration or temporarily discontinue background therapy of mineralocorticoid antagonists (if they are believed to be the most likely cause of hyperkalemia).
- apply all measures outlined for serum potassium > 5.3 and ≤ 5.5 mmol/l*
- repeat serum potassium measurement after 2-3 days
- if serum potassium < 5.5 mmol/l*, consider resumption of study drug at lower dose with repeat serum potassium within 5 days

Serum potassium greater than or equal to 6.0 mmol/L (mEq/L)*

- immediately discontinue study drug
  - confirm serum potassium concentration in a non-hemolyzed sample
  - urgently evaluate participant and treat hyperkalemia as clinically indicated
  - apply all measures outlined for serum potassium > 5.3 and < 6.0 mmol/l (mEq/l)*

No resumption of study drug without individualized case discussion with and permission from ARO medical monitor or his/her designee.

* Or equivalent plasma potassium value

16.5 Appendix 5: Guidelines for the management of blood pressure

Guidelines

1. Investigator should monitor BP closely
2. if symptomatic hypotension occurs:
   a. correct any treatable cause, e.g. hypovolemia
   b. if hypotension persists, any non-disease modifying background antihypertensive drug such as diuretics, calcium channel blockers (CCBs), nitrates, and/or α-blockers, can be down-titrated or stopped first per Investigator's clinical judgement before down-titration of the study drug is considered
   c. it is important to note that dose adjustment of disease-modifying background therapy, e.g., β blockers, or mineralocorticoid antagonists is discouraged under these circumstances, unless they are believed to be the most likely cause of hypotension

If hypotension persists, the study drug should be down-titrated or even temporarily withdrawn. The dose re-challenge and medications adjust guidelines described in Section 6.5.1.1 should be adhered to as much as possible.

16.6 Appendix 6: Holter monitoring

16.6.1 Purpose

To evaluate the impact of sacubitril/valsartan compared with enalapril on the arrhythmia burden in a subset of approximately 400 consecutive participants randomized to the Main Study over a period of 8 months after Randomization.

16.6.2 Objectives

1. To estimate the prevalence of arrhythmias (i.e., premature ventricular contractions [PVC], non-sustained ventricular tachycardia [NSVT], ventricular tachycardia [VT]) in participants with CCC
2. To evaluate the effect of sacubitril/valsartan versus enalapril on the arrhythmia burden from Randomization to Month 8

16.6.3 Endpoints

16.6.3.1 Primary

Composite of reduction in PVC burden, sustained VT, and non-sustained VT episodes at Randomization and Month 8 (arrhythmia burden)

16.6.3.2 Secondary

- Correlation of arrhythmia burden with biomarkers
- Correlation of arrhythmia burden with CV mortality
- Incidence of associated safety events (AEs/SAEs)

16.6.3.3 Exploratory

Incidence of atrial arrhythmia.

16.6.4 Investigational plan

Enrollment in the Holter monitoring assessment will be sequential, with all eligible participants within a participating study site considered for enrollment. Participants who consent to the additional assessment will undergo Holter monitoring at Randomization and at Month 8 post-randomization.

Holter recorders are to be shipped from Libin Cardiovascular Institute of Alberta to national coordinating sites and once recorded shipped directly from sites to Holter Core-lab.

Further details will be provided in the Holter manual.

16.6.5 Data analysis

Summary statistics by treatment arm will be estimated for PVC burden, sustained VT, and non-sustained VT.

The primary endpoint will be analyzed by generalized mixed linear models considering the hierarchical effect of study site and participant.

The correlation of arrhythmia burden with biomarkers, mortality, and associated safety events, and the exploratory analysis of atrial arrhythmia will be analyzed using generalized mixed linear models.

The analyses will be done using R software (R Core Team 2020).

16.6.6 Sample-size

The sample size is estimated based on data available in Table 2 of de Diego et al (2018), which include the following parameters:

- PVC burden (PVC/hour)
- Sustained VT
- Non-sustained VT (NSVT)

It is estimated that approximately 400 participants are needed in order to have adequate 80% power for each parameter separately, acknowledging the limitation that in the reference source used for the calculations (de Diego et al 2018), the data were from the same group of 120 participants treated with angiotensin inhibition alone for 9 months followed by angiotensin-neprilysin inhibition for another 9 months.

16.7 Appendix 7: Magnetic resonance imaging

16.7.1 Purpose

To determine if sacubitril/valsartan is superior to enalapril in reducing fibrosis and improving cardiac structure and function in participants with CCC.

16.7.2 Objective

To examine the changes in cardiac structure, function, and fibrosis after 8 months of treatment with sacubitril/valsartan or enalapril.

16.7.3 Investigational plan

Enrollment in the MRI additional assessment will be sequential with all eligible participants within a participating study site considered for enrollment. Participants with no contraindications to undergoing cardiac MRI and who consent to this additional assessment will undergo cardiac MRI at Randomization and at Month 8 post-randomization.

The additional assessment will include approximately 100 participants from selected study sites. Participants with any contraindication for undergoing cardiac MRI will be excluded.

Further details will be provided in the MRI manual.

16.7.4 Data analysis

Summary statistics will be presented by treatment arm.

The reduction of fibrosis and the improvement of cardiac structure after 8 months of treatment will be analyzed using generalized mixed linear models considering the hierarchical effect of study site and participant.

The analyses will be done using R software (R Core Team 2020).

The coded medical images will be used primarily for the analysis of cardiac structure, function, and degree of fibrosis; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

16.7.5 Sample-size

The effects of sacubitril-valsartan on regression of myocardial fibrosis by MRI is not known. Statistical significant regression of diffuse fibrosis was reported in 36 patients who underwent catheter ablation for atrial fibrillation. Other positive studies that showed statistically significant regression of fibrosis included 35 patients treated with lisinopril for hypertensive heart disease (Brilla et at 2000); 25 patients treated with mineralocorticoid receptor antagonists for dilated cardiomyopathy (Izawa et al 2005); and 34 patients treated with losartan for hypertensive disease (Diez et al 2002).

In an exploratory manner, the inclusion of 50 participants in each arm seems to be enough to evaluate if sacubitril-valsartan can elicit regression of fibrosis detected by MRI.