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LCZ696
sacubitril/valsartan

Clinical Trial Protocol CLCZ696BUS13

A 52 week, open label evaluation of the effects of sacubitril/valsartan (LCZ696) therapy on biomarkers, myocardial remodeling and patient-reported outcomes in heart failure with reduced left ventricular ejection fraction (PROVE-HF)

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List of abbreviations

AAC	Angioedema Adjudication Committee
ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
AE	adverse event
ALT	Alanine Aminotransferase
ARNI	Angiotensin receptor neprilysin inhibitor
AST	Aspartate Aminotransferase
BID	Twice a day
BNP	B-type natriuretic peptide
BUN	Blood urea nitrogen
cGMP	Cyclic guanosine monophosphate
CHF	Chronic heart failure
CFR	US Code of Federal Regulations
CRF/eCRF	(electronic) Case Report/Record Form
CRO	Contract Research Organization
CRT-D	Cardiac resynchronization therapy defibrillator
CRT-P	Cardiac resynchronization therapy pacemaker
CV	cardiovascular
DBP	diastolic blood pressure
DM	diabetes mellitus
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
Echo	echocardiogram
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
EOS	End of study
FAS	Full analysis set
GCP	Good Clinical Practice
HF	heart failure
HFrEF	Heart failure with reduced ejection fraction
hs-Troponin	high sensitivity troponin
HTN	Hypertension
ICF	Informed consent
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	Left atrial
LAVi	Left atrial volume index
LVEF	Left ventricular ejection fraction

LVEDVi	Left ventricular end diastolic volume index
LVESVi	Left ventricular end systolic volume index
LV	Left ventricular
mm Hg	millimeter mercury
MoA	Mechanism of action
MUGA	multi gated acquisition scan
NEP	Neutral endopeptidase
NP	Natriuretic peptide
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
Pg/ml	Picogram per milliliter
RAAS	Renin angiotensin aldosterone system
SAE	Serious Adverse Event
SBP	Systolic blood pressure
sST2	Soluble ST2
SUSAR	Suspected Unexpected Serious Adverse Reactions
UNL	Upper limit of normal
USPI	United States prescribing information/package insert
VAD	Ventricular assistance device
WHF	Worsening heart failure
WoC	Withdrawal of Consent

Glossary of terms

Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Drugs(s) 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 subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch Replaces the term "Period" previously used for NOVDD studies	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in subjects with established disease and in those with newly-diagnosed disease.
Subject/subject ID	A unique number assigned to each subject upon signing the informed consent
Study drug/ treatment	Any single drug or combination of drugs administered to the subject as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Amendment 3

Rationale for amendment

The purpose of Amendment 3 is to remove the interim analysis that was to occur after 300 subjects completed the study. Due to the speed of enrollment into the study, an interim analysis is no longer as feasible or as informative since this analysis would be performed after all of the patients had already been enrolled, and only 3 to 4 months prior to study completion.

All relevant section(s) of the protocol are updated to reflect the removal of the interim analysis.

Additionally, other administrative changes include the following:

- Under List of Abbreviations added "EOS" End of Study.
- Section 2.3 was edited to include "up to".
- Section 6; Table 6-1 Assessment Schedule added (EOS) under visit number 10 to align with section 5.5.2.

Summary of previous amendment 02 (June 2017)

The purpose for Amendment 2 is to add 3 additional exclusion criteria:

- Subjects with a heart transplant or ventricular assistance device (VAD) or intent to transplant (on transplant list) or implant a VAD.
- Subjects with a cardiac resynchronization therapy devices (CRT-P/CRT-D) implanted within 6 months of screening visit.
- Subjects currently taking inotropic agents.

All relevant section(s) of the protocol are updated to reflect the 3 additional exclusion criteria.

Additionally, other administrative changes include the following:

- Administrative changes such as the correction of typographical error have been made throughout the protocol.
- Clarified inclusion criteria #3 and #6 and exclusion #3 and #11.
- Section: 5.4.5: was edited to add clarification to the study titration.
- Section: 6, Table 6-1: Added Dosage Administration record, angioedema and footnote for Assessing CV events.

Summary of previous amendment 01(September 2016)

The purpose for Amendment 1 is to allow for the collection of serum pregnancy testing at both visits 8 and 9 to account for pregnancy testing being performed approximately every 90 days.

All relevant sections(s) of the protocol are updated to reflect the additional collection of serum pregnancy tests.

Additionally, other changes include the following:

- List of Abbreviations: added MUGA multi gated acquisition scan
- Protocol title was update to include "PROVE-HF".
- Protocol Summary: Population and Key Inclusion Criteria #3 was updated to include HFrEF ≤ 40% subjects who are candidates for on-label sacubitril/valsartan treatment per standard of care; added Inclusion criteria #5: LVEF ≤40% via any local measurement within the past 6 months using echocardiography, multi gated acquisition scan (MUGA), CT scanning, MRI or ventricular angiography provided no subsequent study documenting an EF of >40%. If the EF measurement is expressed as a value range, the average of the range endpoint values should be used as the EF and deleted exclusion #7, subjects are require to have a 36-hour washout post-dose of sacubitril/valsartan.
- Protocol Summary: Key exclusion Criteria updated to include exclusion #4 Current or prior treatment with sacubitril/valsartan and #7 was reworded to say "Subjects with diabetes mellitus who are taking aliskiren."
- Protocol Summary: Data Analysis was updated to include the word "clinical".
- Protocol Summary: Efficacy assessments: in the exploratory section was updated to align with section 6.4.2.
- Protocol Summary: Other assessments was updated to align with protocol, "We will examine total Cardiovascular events: All deaths, CV versus non-CV, Sudden versus non-sudden, Resuscitated Sudden Death, Hospitalization for HF and Worsening HF" was deleted.
- Section 3.1: Study Design: under screening epoch paragraph was reworded to say "Subjects will be considered eligible if they are identified as clinically appropriate HFrEF subjects and who are candidates for on-label sacubitril/valsartan treatment per the USPI prescribing information"; under screening epoch sentences 3-5 were moved to section 3.1 under Baseline (Day 1). Under Screening epoch: was reworded to say "Subjects will be screened to assess eligibility requirements and to confirm that subjects meet all study entry criteria and Figure 3-1 was updated to align with study design, deleted 36 hour washout of ACEi prior to baseline.
- Sections 4 and 4.1 was updated to include ≤ 40% to HFrEF and LVEF ≤40% via any local measurement within the past 6 months using echocardiography, multi gated acquisition scan (MUGA), CT scanning, MRI or ventricular angiography provided no subsequent study documenting an EF of >40%. If the EF measurement is expressed as a value range, the average of the range endpoint values should be used as the EF.
- Section 4.2 was updated to deleted previous exclusion #4, subjects are require to have a 36-hour washout post-dose of sacubitril/valsartan and updated to include exclusion #4, "Current or prior treatment with sacubitril/valsartan; and #7 was reworded to say "Subjects with diabetes mellitus who are taking aliskiren."

- Section 5.4.4 was updated to "These subjects will be instructed to wait 36 hours from their last dose of ACEis before taking their first dose of sacubitril/valsartan.
- Section 5.5.3 was updated to replace "Withdrawal of Informed Consent" with "Study Completion".
- Table 6-1: Assessment schedule was updated to include protocol number in header CLCZ696BUS13, updated Safety Laboratory (chemistry/hematology) to align with section 6.5.5.1 and 6.5.5.2; Drug Accountability was update from x to s; being captured on source document and added a column for Unscheduled Visit. Added a row to "Assess of Cardiovascular events" to align with section 8.6.
- Section 6.2 was changed from "date of birth" to "year of birth" to match electronic data capture.
- Section 6.4.2 was added to include "Cardiovascular Events"
- Section 6.5.5.3 was updated by replacing "central lab" with "local lab"; adding "glucose" to ketones; and adding: "Microscopy and WBC and RBC sediments will also be assessed in case of an abnormal dipstick test (central lab)."
- Section 6.5.6 Pregnancy/Assessments of fertility was updated to add visits 8 and 9 to serum pregnancy.
- Section 9.5.1 Secondary variables #3 was updated to add the word "clinical".
- Section 8.6: was removed since a CV events adjudication committee is not required.
- List of abbreviations: added AAC (Angioedema Adjudication Committee).

Protocol summary

Protocol number	LCZ696BUS13
Title	A 52 week, open label evaluation of the effects of sacubitril/valsartan (LCZ696) therapy on biomarkers, myocardial remodeling and patient-reported outcomes in heart failure with reduced left ventricular ejection fraction (PROVE-HF).
Brief title	Effects of sacubitril/valsartan (LCZ696) in heart failure subjects treated as per standard of care.
Sponsor and Clinical Phase	Novartis Clinical Phase IV
Investigation type	Drug
Study type	Interventional, Open-label
Purpose and rationale	The purpose of this study is to determine early and more chronic changes in concentrations of biomarkers related to mechanisms of action (MOA) and effects of sacubitril/valsartan therapy over a period of 12 months, and correlate these biomarker changes with cardiac remodeling parameters, patient-reported outcomes and cardiovascular outcomes. This protocol will allow for evaluation of improved understanding of the interplay between sacubitril/valsartan and biomarkers, remodeling and outcomes, and will carefully assess such relationships within important cohorts of subjects, such as those with low NT-proBNP/BNP at baseline, those naïve to HF therapy, as well as those that are unable to achieve target dose of sacubitril/valsartan. This protocol will also generate a biorepository of well-handled and carefully considered biomarkers, which will allow a better understanding of sacubitril/valsartan MOA
Primary Objective(s)	The primary objective of this study is to examine the association between change in concentration of NT-proBNP and change in structural cardiac measurements (LV end systolic and diastolic volume indices, LVEF, and LA volume index) from baseline to one year.
Secondary Objectives	Examine the association between change in concentration of NT-proBNP and change in structural cardiac measurements (LV end systolic and diastolic volume indices, LVEF, and LA volume index) from baseline to 6 months overall in subgroups of interest, these subgroups are: 1. Subjects with HFrEF and “low” NT-proBNP (<600 if not hospitalized or <400 if hospitalized) or “low” BNP (<150 if not hospitalized, <100 if hospitalized) at baseline (Ambrosy, 2012).

	2. Subjects with new onset HF and/or RAAS naïve (Fonarow, 2010). 3. Subjects who are not receiving the target sacubitril/valsartan dose (McMurray, 2014). Examine the association between the change in NT-proBNP concentrations and patient-reported outcomes from the KCCQ-23 during a year of follow up.
Study design	Multi-center, Open-label, single arm
Population	The study population will consist of outpatient male and female subjects, ≥ 18 years of age, with HFrEF≤ 40%. The goal is to have a total of approximately 830 subjects enrolled, in approximately 100 centers in the United States. At the time of enrollment, subjects will have been identified by their primary care physician or cardiologist as a candidate for treatment with sacubitril/valsartan as per USPI and meeting all other inclusion and none of the exclusion criteria.
Key Inclusion criteria	Subjects eligible for inclusion in this study have to fulfill all of the following criteria: 1. Written informed consent must be obtained before any assessment is performed. 2. Men and women ≥ 18 years of age. 3. LVEF ≤ 40% subjects who are candidates for on-label sacubitril/valsartan treatment per standard of care. 4. NYHA Functional class II-IV. 5. LVEF ≤40% via any local measurement within the past 6 months using echocardiography, multi gated acquisition scan (MUGA), CT scanning, MRI or ventricular angiography provided no subsequent study documenting an EF of >40%. If the EF measurement is expressed as a value range, the average of the range endpoint values should be used as the EF. 6. If a subject is on a loop diuretic, they must be on a stable dose for 2 weeks prior to baseline.
Key Exclusion criteria	1. History of hypersensitivity to any of the study drugs, including history of hypersensitivity to drugs of similar chemical classes, or allergy to ACEIs, ARBs, or NEP inhibitors as well as known or suspected contraindications to the study drugs. 2. History of angioedema drug related or otherwise. 3. Requirement of treatment with either ACE inhibitor and/or ARB. 4. Subjects with a heart transplant or ventricular assistance device (VAD) or intent to transplant (on transplant list) or implant a VAD. 5. Subjects with a cardiac resynchronization therapy devices (CRT/CRT-D) implanted within 6 months of screening visit. 6. Subjects who are currently taking inotropic agents. 7. Current or prior treatment with sacubitril/valsartan. 8. Subjects taking medications prohibited by the protocol (Section 5.4.8).

	9. Subjects with diabetes mellitus who are taking aliskiren. 10. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days until the expected pharmacodynamic effect has returned to baseline, whichever is longer. 11. Concomitant use of nesiritide. 12. Bile acid sequestering agents such as cholestyramine or colestipol are prohibited to avoid interference with study drug absorption. 13. Any hospital admission/discharge related to heart failure within 2 weeks prior to baseline. 14. The use of outpatient or inpatient i.v. diuretic therapy within 2 weeks prior to baseline. 15. Enrollment in another clinical trial within 30 days of screening. 16. Potassium > 5.2 mEq/L at screening 17. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within one year. 18. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test. 19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 7 days after stopping of study medication. Highly effective contraception methods include: 20. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception 21. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment 22. Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject 23. Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) 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 investigational drug. 24. Sexually active males must use a condom during intercourse while taking drug and for 7 days after stopping study medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via

	seminal fluid.
Study treatment	All eligible subjects will receive sacubitril/valsartan (LCZ696). The study treatment will be provided for the duration of the trial from baseline (Day 1) through visit 10 (Day 365).

Efficacy assessments	The efficacy variables are:
	Primary:
	• Change in concentration of NT-proBNP from baseline to one year
	• Change in LVESVi, LVEDVi, LVEF, and LA volume index (LAVi) from baseline to one year
	Secondary:
	• Change in concentration of NT-proBNP from baseline to 6 months
	• Change in LVESVi, LVEDVi, LVEF, and LA volume index (LAVi) from baseline to 6 months
	• Change in KCCQ-23 baseline to one year
	Exploratory:
	• Change in concentration of other more stable biomarkers reflecting mechanism of action of sacubitril/valsartan and/or HF prognosis ("efficacy" biomarkers) from baseline-to-interim study visit, across one year of management, and examined as a function of change in echocardiographic variables
	• Total cardiovascular events following sacubitril/valsartan initiation and up-titration, during the follow up period of 12 months. The CV events include:
	• All deaths
	  • CV versus non-CV
	  • Sudden versus non-sudden
	• Resuscitated Sudden Death
	• Hospitalization for HF
	• Worsening HF
	• In a subset of subjects (N=up to 300) with collected and processed samples:
	1. Effects of sacubitril/valsartan on concentrations of BNP, as determined by several different assays used in clinical practice.
	2. Change in concentration of labile biomarkers thought to reflect the mechanism of action of sacubitril/valsartan ("MOA" biomarkers) from baseline-to-interim study visit, across one year of management, and examined as a function of change in echocardiographic variables.

Key safety assessments	• Physical examinations • Monitoring of laboratory biomarkers in blood (plasma/serum) • Echocardiograms

	• Adverse event monitoring
Other assessments	• An assessment of subject reported outcomes is planned in this trial using Quality of life, based on the Clinical Score of the KCCQ-23.
Data analysis	Pearson's correlation coefficient and its two-sided 95% confidence interval (CI) to examine the association between change in log-transformed NT-proBNP and LVESVi, LVEDVi, LVEF, and LAVi from baseline to one year and baseline to 6 months will be calculated Similar correlation coefficients and CIs will be calculated for the following subgroups: • Subjects with *de novo* HF (naïve to ACE inhibitor or ARB therapy) and those with previously established HF. • Subjects with NT-proBNP values <600 pg/mL (or 400 pg/mL if hospitalized for HF within 1 year) at the time of drug initiation, and those with higher values. • In those not receiving the target sacubitril/valsartan dose and those achieving target dose. • In those with an NT-proBNP concentration <1000 pg/mL at Month 12 and those with NT-proBNP ≥1000 pg/mL at the same time point. • As a function of time from baseline to an NT-proBNP value of <1000 pg/mL for subjects with a baseline value >=1000 pg/mL (percentiles of response time). • As a function of time spent with NT-proBNP concentration <1000 pg/mL across study visits (percentiles of response time). • The primary analysis of the primary efficacy variables will be based on the Full Analysis Set. An analysis of variance will be done to compare the mean change in the KCCQ-23 clinical summary score between the groups of subjects with NT-proBNP<1000 pg/mL and NT-proBNP>=1000 pg/mL at Month 12. Propensity score adjustments will be used in the comparison of treatment groups. We would like to estimate the correlation coefficient between change in log NT-proBNP and each structural cardiac measurement overall and in each subgroup of interest with a precision (half-width of the confidence interval (CI)) of at least 0.15 for a 2-sided 95% CI. The subgroups of interest are: (1) subjects with HFrEF and "low" NT-proBNP (<600 if not hospitalized or <400 if hospitalized) or "low" BNP (<150 if not hospitalized, <100 if hospitalized) at baseline, (2) subjects with new onset HF and/or RAAS naïve, and (3) subjects who are not receiving the target sacubitril/valsartan dose. It is estimated that these subgroups will represent approximately 25%, 20% and 30% of the study population, respectively. Assuming, the population correlation coefficient of -0.35 for the overall study sample and within each subgroup, the smallest sample size that would yield a precision of at least 0.15 for the estimated correlation coefficient would be n=133. Accounting for assumed 20% drop-out rate, 166 patients would be required. If the n=166 was the smallest subgroup of interest (20% of

	the overall study population), an overall sample size of 830 would be required to enroll in this study. For any other subgroup with more than 166 patients will yield precision smaller than 0.15 for the estimated correlation coefficient. For the overall sample size of N=830 patients the precision of the estimate of correlation coefficient would be 0.07 (PASS 2008).
Key words	Heart failure, reduced left ventricular ejection fraction, cardiac remodeling parameters.

1 Introduction

1.1 Background

Globally, heart failure (HF) is reaching epidemic proportion, leading to substantial efforts to understand the biology of HF, improve recognition of its presence, and more optimally manage subjects so-affected. As such strides have been made in the study of risk factors for progressive HF, as well as the means by which to recognize and treat it.

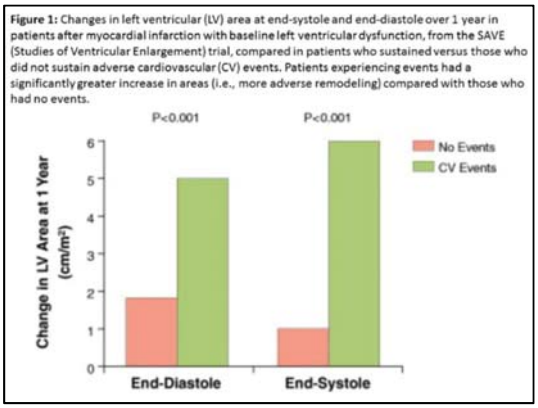


Figure 1: Changes in left ventricular (LV) area at end-systole and end-diastole over 1 year in patients after myocardial infarction with baseline left ventricular dysfunction, from the SAVE (Studies of Ventricular Enlargement) trial, compared in patients who sustained versus those who did not sustain adverse cardiovascular (CV) events. Patients experiencing events had a significantly greater increase in areas (i.e., more adverse remodeling) compared with those who had no events.

A fundamental goal in the management of subjects with HF and reduced ejection fraction (HFrEF) is the prevention of myocardial remodeling. As noted by Konstam, 2011, myocardial remodeling is central in the pathophysiology of advancing HF; for example, subjects with cardiovascular (CV) events in the Survival and Ventricular Enlargement study (Konstam 2011) of HFrEF demonstrated considerably greater degrees of myocardial remodeling compared to those without events (Figure 1).

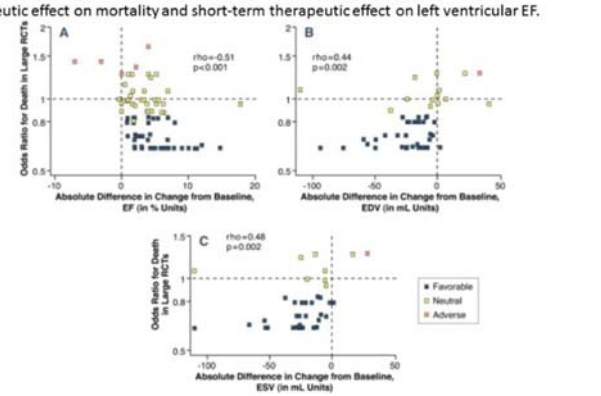


Figure 2: Quantitative relationship between drug/device effects on ejection fraction (EF), end-diastolic volume (EDV), end-systolic volume (ESV), and mortality in patients with heart failure and left ventricular dysfunction. Each data point represents a placebo-corrected change in EF **(A)**, EDV **(B)**, or ESV **(C)** from an individual remodeling trial plotted against the mortality odds ratio for the specific therapy. There was a significant correlation between longer term therapeutic effect on mortality and short-term therapeutic effect on left ventricular EF.

The benefit of contemporary HF therapies appears to be in part reflective of the anti-remodeling benefits of such agents, including agents blocking the renin angiotensin aldosterone system (Figure 2). Unfortunately, however, risk for remodeling of the myocardium may be challenging to recognize.

Biomarkers are increasingly measured as a tool to diagnose, establish prognosis, as well as to monitor or guide HF therapy. The gold standard HF biomarkers are B-type natriuretic peptide (BNP) and its amino-terminal pro-fragment equivalent (NT-proBNP). Concentrations of BNP and NT-proBNP not only provide unique diagnostic information for HF, but also allow for an understanding of the underlying biology of HF, including identifying the presence and severity of myocardial remodeling. As articulated by Yancy 2013, both peptides have Class I, level of evidence. A support in current clinical practice guidelines for diagnosis and prognosis in HF (Yancy 2013) and in 2014, more than 20 million measurements of these two peptides were made.

With well-established links between change in the natriuretic peptides during HF therapy and both myocardial remodeling as well as outcomes, increasingly, clinicians turn to biomarkers such as BNP or NT-proBNP for decision making regarding prognosis and therapy changes in subjects so affected (Ambrosy 2012; Januzzi 2011; Masson 2006).

It is now widely accepted that among subjects with HFrEF an NT-proBNP concentration <1000 pg/mL during therapy titration is associated with significantly less likelihood for deleterious LV remodeling than subjects with concentrations above this value (table 1) (Konstam 2011), and lower NT-proBNP concentrations are also associated with better outcome as well, (Januzzi 2011; Masson 2006). Furthermore, as opposed to a single measurement, across serial measurement, the time spent with an NT-proBNP <1000 pg/mL over a one year period was reported to be even more strongly associated not only with superior outcome (Gaggin 2013), but also with more robust improvement in LV and left atrial (LA) size and function (Weiner 2013).

Table 1: Risk for LV remodeling as a function of achieved NT-proBNP concentrations following intensification of therapy for HFrEF.

	Hazard ratio[a]	95% CI	*P*-value
Increase in LVEDVi	1.43	1.10–1.86	0.007
Increase in LVESVi	1.54	1.10–1.91	0.01
Fall in LVEF	1.53	1.12–1.89	0.02

CI, confidence interval; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; NT-proBNP, N-terminal pro B-type natriuretic peptide.
[a]Hazard ratio refers to risk for remodelling per log-unit of NT-proBNP at the end of the study. NT-proBNP was entered as log-transformed due to non-normality. Model adjusted for baseline log-transformed NT-proBNP, age, New York Heart Association symptom severity, prior myocardial infarction, diabetes mellitus, ratio of early transmitral peak velocity to early diastolic peak annular velocity (E/E') >15 at baseline, and percentage titration of aldosterone antagonists during the trial.

Remodeling metrics include LVEF as well as measures of both systolic and diastolic volumes, LV end systolic volume index (LVESVi) and LV end diastolic volume index (LVEDVi). Change in each has been used as the gold standard for LV reverse remodeling.

Beyond the clinical value of BNP or NT-proBNP, measurement of circulating HF biomarkers may also be helpful to understand mechanism of benefit of HF therapies and provide important insight to mechanism of action (MOA) of such therapies.

Preliminary studies

In the landmark Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality in HF [PARADIGM-HF] (McMurray 2014) study, changes in both BNP and NT-proBNP were seen during the sacubitril/valsartan (LCZ696) run-in period, at 4 weeks, and 8 months (Packer 2015): treatment with sacubitril/valsartan led to substantial reduction in NT-proBNP, thought to be reflective of benefit of the drug. Beyond this, it is yet unclear whether NT-proBNP reduction predicted other favorable effects in therapy of HFrEF such as reverse LV remodeling. Through inhibition of neprilysin by sacubitril active metabolite, sacubitril/valsartan led to a rise in BNP concentration. The ramification of such increase in BNP concentration relative to diagnostic and prognostic accuracy remains unclear; for example, it is unknown if measurement of BNP will retain association/correlation with LV remodeling and/or prognosis. This may have substantial ramification regarding the future of BNP, the most widely measured natriuretic peptide in the United States.

Limitations of the PARADIGM-HF biomarker experience include only limited time points for blood sampling, which hampers ability to examine short and longer term changes in biomarkers following initiation and up titration of sacubitril/valsartan. As well, only one BNP

assay was assessed in PARADIGM-HF. It is thus uncertain whether other commercially available BNP assays utilizing different antibody pairs will demonstrate the same effect from neprilysin inhibition. As BNP is widely used for diagnostic and prognostic evaluation, understanding effects of sacubitril/valsartan on representative BNP assays is of substantial importance. Furthermore, it remains unclear whether effects of sacubitril/valsartan differ on biomarker profiles of subjects naïve to HF therapy ("new starts") or in those with NT-proBNP/BNP concentrations below those used for inclusion in PARADIGM-HF. Crucially, no data exist regarding effects of sacubitril/valsartan on LV remodeling. Lastly, because of challenges in handling of blood samples, several candidate markers of sacubitril/valsartan MOA could not be measured in the PARADIGM-HF trial or biorepository.

1.2 Purpose

The purpose of this study is to determine early and more chronic changes in concentrations of biomarkers related to mechanisms of action (MOA) and effects of sacubitril/valsartan therapy over a period of 12 months, and correlate these biomarker changes with cardiac remodeling parameters, patient-reported outcomes and cardiovascular outcomes.

2 Study objectives and endpoints

2.1 Primary objective(s)

The primary objective of this study is to examine the association between change in concentration of NT-proBNP and change in structural cardiac measurements (LV end systolic and diastolic volume indices, LVEF, and LA volume index) from baseline to one year.

2.2 Secondary objective(s)

- Examine the association between change in concentration of NT-proBNP and change in structural cardiac measurements (LV end systolic and diastolic volume indices, LVEF, and LA volume index) from baseline to 6 months overall in subgroups of interest, these subgroups are:
  1. Subjects with HFrEF and "low" NT-proBNP (<600 if not hospitalized or <400 if hospitalized) or "low" BNP (<150 if not hospitalized, <100 if hospitalized) at baseline (Ambrosy 2012).
  2. Subjects with new onset HF and/or RAAS naïve (Fonarow 2010).
  3. Subjects who are not receiving the target sacubitril/valsartan dose (McMurray 2014).
- Examine the association between the change in NT-proBNP concentrations and patient-reported outcomes from the KCCQ-23 during a year of follow up.

2.3 Exploratory objectives

- To examine change in concentration of other efficacy, HF prognosis or mechanism of action biomarkers collected in the full subject population from baseline-to-interim study visit, across one year of management, and examined as a function of change in echocardiographic parameters.

- To examine the association between cardiovascular events following sacubitril/valsartan initiation and up-titration, during the follow up period of 12 months, with change in "efficacy" biomarkers and echocardiographic remodeling indices. The CV events include:
  1. WHF
  2. Heart failure hospitalization
  3. CV death
- In a subset of subjects (N=up to 300) with carefully-collected and processed labile mechanism of action (MOA) biomarkers:
  - To examine effects of sacubitril/valsartan on concentrations of BNP, as determined by several different assays used in clinical practice.
  - To examine change in concentration of MOA biomarkers from baseline-to-interim study visit, across one year of management, and examined as a function of change in echocardiographic variables.

3 Investigational plan

3.1 Study design

This study uses an open-label, single-arm design. The study duration is a maximum of 52 weeks (365 days). A study cohort of approximately 830 subjects will be enrolled. Subjects will be considered eligible if they are identified as clinically appropriate HFrEF subjects and who are candidates for on-label sacubitril/valsartan treatment per the USPI prescribing information.

Screening epoch

Subjects will be screened to assess eligibility requirements and to confirm that subjects meet all study entry criteria. At screening, safety blood and urine samples will be collected and submitted to the central laboratory.

Baseline (Day 1)

Sacubitril/valsartan will be dispensed to eligible subjects at Visit 2 (Day 1/baseline). Initial dosing and titration will be done according the United States Prescribing Information (USPI). Subjects that have been treated with ACEi before the study will require a 36-hour wash out period before starting sacubitril/valsartan treatment. These subjects will be instructed to wait 36 hours from their last dose of ACEi before taking their first dose of sacubitril/valsartan. Their first dose of sacubitril/valsartan will therefore be approximately 36 hours from last dose of ACEi.

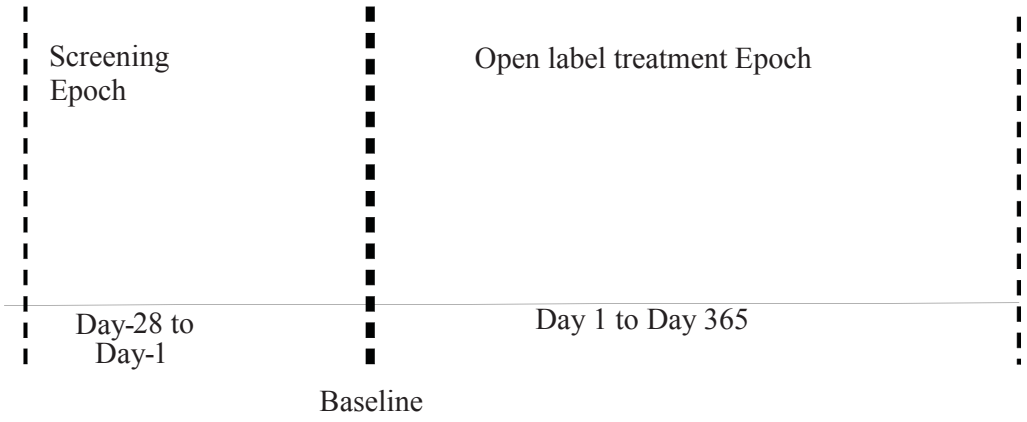
Open Label treatment epoch

The open label treatment period duration is 12 months. Visits will occur every 2 weeks until Visit 6 (Day 60) and then at 7, 8, 9 and 10 (end of study).

Titration of study treatment initiated at Visit 2 (baseline) will be done according to the USPI. Deviation from the titration schedule or dose adjustments will only be allowed if indicated per protocol defined safety and tolerability criteria section 5.4.5 and investigator judgment, if the

investigator believes that adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern. Protocol required assessments for each visit will be done according to the schedule of assessments (Table 6-1).

Figure 3-1 Study design



3.2 Rationale for study design

Open questions about sacubitril/valsartan exist; this protocol will address some of the important gaps in knowledge regarding this novel drug. Measurement of biomarkers BNP and NT-proBNP are now routine assessments in standard care for HF subjects. The use of these biomarker has a Class I, level of evidence A for prognosis in clinical practice guidelines (Yancy 2013). Biomarkers (including NT-proBNP) are well-associated and correlated with myocardial remodeling as well (Weiner 2013).

It is understood that sacubitril/valsartan has substantial effects on NT-proBNP and BNP, but these effects are fundamentally different. There is a critical need to provide greater clarity for clinicians on how to interpret information on both biomarkers during treatment with sacubitril/valsartan, given the increasing frequency of therapy monitoring with natriuretic peptides. For BNP, mis-interpretation of a "rise" in the values could theoretically lead to mis-treatment of subjects. This could also result in clinician confusion regarding sacubitril/valsartan (ie. - it could be thought of as "toxic" and leading to rise in BNP). Another possibility is frustration with either BNP or sacubitril/valsartan, creating risk that they may cease measuring the biomarker or using the drug). It is unclear if BNP will impart useful information regarding remodeling and prognosis when subjects are treated with

sacubitril/valsartan. It is also unclear what effect sacubitril/valsartan has on BNP using different BNP assays in broad clinical use.

While sacubitril/valsartan treatment was shown in the PARADIGM-HF trial to have an early and sustained benefit in mortality reduction and HF hospitalization in HFrEF subjects compared to treatment enalapril and guideline-directed medical therapy, clinical data are lacking regarding whether sacubitril/valsartan therapy fosters significant LV or LA remodeling (McMurray 2014). As reported by Konstam 2011 degree of myocardial remodeling following HF therapy strongly predicts benefit of such therapies (Konstam 2011). Examining the inter-relationship between biomarkers, echocardiographic remodeling, and clinical (and subject-reported) outcomes would provide substantial understanding regarding mechanism of benefit from sacubitril/valsartan therapy.

In view of this significant treatment benefit demonstrated in the PARADIGM-HF trial, Novartis has provided guidance for company-supported trials that the randomized period for assessing sacubitril/valsartan against an active comparator may not exceed 12 weeks. The intermediate-term and chronic biomarker changes, as well as the structural heart reverse remodeling endpoints being evaluated in this trial require a study period of 12 months. Because this exceeds the 12 week guidance, it precludes a two arm study design with an active comparator, and trial needs dictate a single arm design.

This protocol will allow for evaluation of improved understanding of the interplay between sacubitril/valsartan and biomarkers, remodeling and outcomes, and will carefully assess such relationships within important cohorts of subjects, such as those with low NT-proBNP/BNP at baseline, those naïve to HF therapy, as well as those that are unable to achieve target dose of sacubitril/valsartan.

This protocol will also generate a biorepository of well-handled and carefully considered biomarkers, which will allow a better understanding of sacubitril/valsartan MOA.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

Sacubitril/valsartan, 97/103mg BID was selected as the target dose and is the USPI approved target dose. This dose of sacubitril/valsartan delivers similar exposures of valsartan as Diovan 160 mg BID, the maximal approved Diovan dose for heart failure and the dose recommended in international guidelines for the treatment of heart failure. In addition, biomarker analysis (increase in ANP and cGMP) indicates that this sacubitril dose delivers approximately 90% of its maximal neutral endopeptidase (NEP) inhibition. Dosing with 97/103 mg twice daily is to ensure sustained NEP inhibition over 24 hours, which is thought to be critical for subjects with heart failure.

As this is a single-arm open label study design, all subjects will be treated with sacubitril/valsartan.

3.4 Rationale for choice of comparator

Not applicable.

3.5 Risks and benefits

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

Experience in the PARADIGM-HF trial, both in the run-in period as well as the double-blind randomization period, indicated that the major risks associated with the treatment of sacubitril/valsartan are renal dysfunction, hyperkalemia, and hypotension. Results from the TITRATION study indicated that subjects who are ACE or ARB naïve are at an increased risk of experiencing these adverse events.

In this study, the risk of experiencing renal dysfunction, hyperkalemia, and hypotension are mitigated by appropriate up-titration of the drug every two weeks according to the USPI. The risks are further mitigated by appropriate inclusion and exclusion criteria. Subjects entering into the study will have their BP evaluated and be treated with sacubitril/valsartan in accordance with the USPI.

Sacubitril/valsartan may also cause angioedema. The risk of developing angioedema is increased if subjects take both an ACEi and sacubitril/valsartan. To decrease this risk, all subjects commencing the open-label treatment period will undergo a 36 hour wash out period prior to starting sacubitril/valsartan to minimize the interaction between an ACEi and sacubitril/valsartan in potentiating the development of angioedema.

All subjects will be allowed to continue receiving the rest of their background cardiovascular (CV) medications throughout the study. Subjects will be enrolled only after the investigator has confirmed the subject is on stable treatment with guideline-directed therapy for HFrEF, other than ACEis and ARBs, which will ensure that subjects are receiving appropriate treatment for their heart failure.

In the PARADIGM-HF study, sacubitril/valsartan reduced the risk of CV death and HF hospitalization and due to these significant results, sacubitril/valsartan is now indicated to reduce these risks in subjects with chronic heart failure (NYHA class II-IV) and reduced ejection fraction.

4 Population

The study population will consist of outpatient male and female subjects, ≥ 18 years of age, with HFrEF ≤ 40%. The goal is to have a total of approximately 830 subjects enrolled, in approximately 100 centers in the United States. At the time of enrollment, subjects will be considered eligible if they are identified as clinically appropriate HFrEF subjects and eligible to receive sacubitril/valsartan per the USPI prescribing information., as well as meeting all other inclusion and none of the exclusion criteria.

4.1 Inclusion criteria

Based on the USPI for sacubitril/valsartan, subjects eligible for inclusion in this study must fulfill all of the following criteria at screening and baseline:

1. Written informed consent must be obtained before any assessment is performed.
2. Men and women ≥ 18 years of age.

3. LVEF ≤ 40% subjects who are candidates for on-label sacubitril/valsartan treatment per standard of care.
4. NYHA Functional class II-IV.
5. LVEF ≤40% via any local measurement within the past 6 months using echocardiography, multi gated acquisition scan (MUGA), CT scanning, MRI or ventricular angiography provided no subsequent study documenting an EF of >40%. If the EF measurement is expressed as a value range, the average of the range endpoint values should be used as the EF.
6. If a subject is on a loop diuretic, they must be on a stable dose for 2 weeks prior to baseline.

4.2 Exclusion criteria

Subjects fulfilling any of the following criteria, **at screening and prior to dispensing of study drug,** are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects/subjects.

1. History of hypersensitivity to any of the study drugs, including history of hypersensitivity to drugs of similar chemical classes, or allergy to ACEIs, ARBs, or NEP inhibitors as well as known or suspected contraindications to the study drugs.
2. History of angioedema drug related or otherwise.
3. Requirement of treatment with either ACE inhibitor and/or ARB.
4. Subjects with a heart transplant or ventricular assistance device (VAD) or intent to transplant (on transplant list) or implant a VAD.
5. Subjects with a cardiac resynchronization therapy devices (CRT/CRT-D) implanted within 6 months of screening visit.
6. Subjects who are currently taking inotropic agents.
7. Current or prior treatment with sacubitril/valsartan.
8. Subjects taking medications prohibited by the protocol (Section 5.4.8).
9. Subjects with diabetes mellitus who are taking aliskiren.
10. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
11. Concomitant use of nesiritide.
12. Bile acid sequestering agents such as cholestyramine or colestipol are prohibited to avoid interference with study drug absorption.
13. Any hospital admission/discharge related to heart failure within 2 weeks prior to baseline.
14. The use of outpatient or inpatient i.v. diuretic therapy within 2 weeks prior to baseline.
15. Enrollment in another clinical trial within 30 days of screening.
16. Potassium > 5.2 mEq/L at screening.
17. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within one year.

18. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 7 days after stopping of study medication. Highly effective contraception methods include:
    a. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    c. Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    d. Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
    e. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.
20. Sexually active males must use a condom during intercourse while taking drug and for 7 days after stopping study medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

5 Treatment

5.1 Study treatment

5.1.1 Investigational drug

All eligible subjects will receive open label sacubitril/valsartan. Sacubitril/valsartan is supplied as unscored, ovaloid, film-coated tablets in the following strengths:

Table 5-1 Open label treatment epoch

Treatment	Number of Subjects	Minimum dose	Median	Maximum dose	Frequency	Formulation	Admin. Route
Open-label, sacubitril/valsartan	830	24/26 mg	49/51 mg	97/103 mg	BID	Tablet	Oral

*Investigational product labeling for sacubitril/valsartan dose levels is based on the total contribution of both components of sacubitril/valsartan and reads, 50 mg, 100 mg and 200 mg. This is equivalent to the sacubitril/valsartan dose levels 24/26 mg, 49/51 mg and 97/103 mg, respectively.

Table 5-2 Treatment dose levels epoch

Dose Level	sacubitril/valsartan
1	24/26 mg BID
2	49/51 mg BID
3	97/103 mg BID

*Investigational product labeling for sacubitril/valsartan dose levels is based on the total contribution of both components of sacubitril/valsartan and reads, 50 mg, 100 mg and 200 mg. This is equivalent to the sacubitril/valsartan dose levels 24/26 mg, 49/51 mg and 97/103 mg, respectively.

Open-label sacubitril/valsartan will be packaged and labeled by the sponsor in accordance with the US Code of Federal Regulation governing handling of investigational treatments, and will be dispensed by the study physician. Open-label treatment will be provided through the duration of the trial. Adjustment of the sacubitril/valsartan dose levels may be increased on an every 2-4 week basis per USPI to the desired target maintenance dose of 97/103 mg or increased within a 1-2 week time period based on clinical need and/or investigator judgment.

Bottles/blister packs will be numbered and assigned via an interactive voice response system (IRT).

5.1.2 Additional treatment

No additional treatment beyond the investigational drug are included in this trial.

5.2 Treatment assignment

Subjects will receive sacubitril/valsartan (LCZ696) on Day 1. The initial dose will be determined by the investigator and per the approved indication described in the USPI. The three doses available are: 24/26 mg (Dose Level 1), 49/51mg (Dose Level 2) and 97/103mg (Dose Level 3).

5.3 Treatment blinding

This is an open label study.

5.4 Treating the subject

The Novartis Medical Monitor may be contacted at any time during the study regarding trial related medical questions or problems.

5.4.1 Subject numbering

Each subject is uniquely identified by a Subject Number which is composed by the 4-digit site number (e.g., 0501, 0502 etc.) assigned by Novartis and a 3-digit sequential number assigned by the investigator (e.g., 001, 002, etc.). Hence a 7-digit study subject identification number, e.g., 0501-001. Once assigned to a subject, the Subject Number will not be reused.

Upon signing the informed consent form, the subject is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the

assigned subject study identification number along with the requested identifying information for the subject to register them into the IRT. The site will enter this number on the electronic case report form (eCRF) in the electronic data capture system (EDC).

If the subject fails to be assigned to treatment for any reason, the IRT must be notified within 2 days that the subject was not assigned to treatment. The reason for not being assigned to treatment will be entered on the Screening Phase Disposition eCRF.

5.4.2 Dispensing the study drug

Novartis will supply each study site with open-label treatment in clinical trial packaging. The study drug packaging has a 2-part label. A unique number is printed on each part of this label which corresponds to one "Dose Level. Investigator staff will identify the study drug package(s) to dispense to the subject by contacting the IRT. Immediately before dispensing the package to the subject, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number.

5.4.3 Handling of study and additional treatment

No additional treatment is provided as part of the study.

5.4.3.1 Handling of study treatment

Investigational 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 designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Medication labels will include storage conditions but no information about the subject 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 site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at each study visit and 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 the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.4.3.2 Handling of additional treatment

Not applicable.

5.4.4 Instructions for prescribing and taking study treatment

The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's

safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

All medication for the duration of the study will be provided by Novartis. Eligible subjects will receive sacubitril/valsartan open label treatment on the first day of treatment at baseline (Day 1).

Initial dose at Day 1 will be determined by the principal investigator according to the USPI.

Subjects that have been treated with ACEi before the study will require a 36-hour wash out before starting sacubitril/valsartan treatment. These subjects will be instructed to wait 36 hours from their last dose of ACEis before taking their first dose of sacubitril/valsartan. Their first dose of sacubitril/valsartan will therefore be approximately 36 hours from last dose of ACEi.

Titration of the dosage will be performed per USPI at 2 to 4 week intervals as clinically tolerated until maximal tolerated or target dosage is achieved.

Study medication should be taken with a glass of water with or without food. If the subject misses taking any study drug dose, he/she should take it as soon as possible, unless it is within

4 hours of the scheduled dosing time. In this case, the subject should skip the missed dose and return back to his/her regular study drug administration schedule.

All dosage prescribed and dispensed to the subject and all dose changes during the study must be recorded in the IRT and on the Dosage Administration Record eCRF.

5.4.5 Permitted dose adjustments and interruptions of study treatment based on safety and tolerability

Every attempt should be made to maintain subjects on the target study drug dose level for as long a duration as possible throughout the study. If, however, in the opinion of the investigator, a subject is unable to tolerate the protocol-specified target dose, the investigator should consider whether dose adjustments of concomitant medications may rectify the situation before reducing the dose of study treatment. If adjustment of the 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, interrupt study drug temporarily or permanently discontinue study drug at his/her discretion. Subjects may restart study drug at any dose level following an interruption of treatment, based on investigator judgment. If study drug is permanently discontinued, the subject should return to the clinic as soon as possible to complete an end of study visit.

Study drug dose level adjustments should be mainly based on overall safety and tolerability with special focus on hyperkalemia, symptomatic hypotension and clinically significant decrease in eGFR/increase in serum creatinine (defined as a serum creatinine of ≥0.5mg/dl with at least a 25% decrease in eGFR).

Table 5-3 Safety and tolerability guidance for dose adjustments

Parameter	Criteria
Potassium level	K > 5.3 mEq/L
Kidney function	• eGFR reduction ≥ 35% compared to baseline; OR, serum creatinine increase of ≥0.5mg/dl with at least a 25% decrease in eGFR
Blood pressure	• Symptomatic hypotension or SBP < 90 mmHg
Adverse events (AEs) or conditions	• Postural symptoms or any conditions that preclude continuation according to the investigator's judgment

All study treatment dose changes must be recorded on the Dosage Administration Record eCRF.

1. Adjust Concomitant Medications

Dose adjustments/elimination of concomitant medications may remedy the situation before reducing the dose of study treatment. If adjustment of the concomitant medications is not possible or does not alleviate the side effects of concern, THEN;

2. Adjust Study Treatment Dose Level

Down-titrate study treatment at the investigator discretion to any dose level. The subject may continue receiving the lower dose level for a recommended period of 1 to a maximum of 4 weeks.

Once stable, the subject should be re-challenged with up-titration to the next higher dose level in an attempt to gradually bring the subjects back to the target study treatment dose level (Dose level 3).

The investigator may choose any dose level for down-or up- titration according to his or her clinical judgment.

3. Study drug restart after temporary treatment interruption

Patients that have had a temporary interruption of study drug may re-start treatment at the most appropriate and allowable dose level per investigator medical judgment.

If tolerated, the subject should be titrated up to any dose level every 1 to 4 weeks, as per the investigator's judgment.

In some instances, Dose Level 1 or 2 could be maintained if the investigator considers that the subject's condition would not allow any further up-titration to the target dose of study medication (Dose Level 3). In this case, it would be acceptable to maintain the subject at Dose Level 1 or 2, whichever is the higher and tolerated dose level by the subject, but reasons for not getting to Dose Level 3 needs to be captured in the eCRF.

Should the subject not tolerate the re-start study drug dose level, he/she may be down-titrated again (if appropriate) or discontinued from study treatment.

4. Stopping Study Treatment

If needed, the study treatment may be permanently discontinued. In this case, the subject should return to the clinic as soon as possible for an end of study visit. All assessments from the final visit (Visit 10) in the visit schedule of assessments (Table 6-1) must be completed and recorded in the eCRF. See Section 5.5.2.

5.4.6 Rescue medication

Subjects may receive open-label ACEIs and/or ARBs during the study ONLY if the study medication has been discontinued either temporarily or permanently. A 36 hour wash-out period is required when switching from or to an ACE inhibitor. Use of rescue medication must be recorded on the concomitant medication eCRF.

5.4.7 Concomitant medication

The investigator must instruct the subject to notify the study site about any new medications he/she takes after the subject was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded in the concomitant medications eCRF or Surgical and Medical Procedures eCRF as appropriate.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before enrolling a subject or allowing a new medication to be started.

Other heart failure and cardiovascular medication

If a subject's condition warrants any change in concomitant heart failure or cardiovascular medications, changes may be made at the investigator's discretion.

Oral diuretics may be used and may be adjusted throughout the study duration at the discretion of the investigator.

Medications and substances known to raise potassium levels

Potassium sparing diuretics, potassium supplements, aldosterone antagonists, and any other medications known to raise potassium levels should be used with caution while the subject is receiving study medication due to the increased possibility of occurrence of hyperkalemia (please refer to Appendix 2). Salt substitutes containing potassium chloride are also to be avoided when possible. Potassium levels should be monitored regularly especially in those who are receiving these medications.

Concomitant administration of renin inhibitors, such as aliskiren, is prohibited in subjects with diabetes mellitus.

Phosphodiesterase-5 (PDE-5) inhibitors

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

Nesiritide and intravenous nitrates

The concomitant admission of sacubitril/valsartan with nesiritide or intravenous nitrates has not been studied. Given biological interaction between sacubitril and BNP, concomitant use of nesiritide (recombinant BNP) should be avoided during the study.

Other medications

Bile acid sequestering agents such as cholestyramine or colestipol are prohibited to avoid possible interference with study drug absorption.

5.4.8 Prohibited medication

Use of the treatments displayed in Table 5-4 is NOT allowed during the study.

Table 5-4 Prohibited medication

Medication	Prohibition period	Action taken
ACEIs Inhibitors: benazepril, enalapril, Lisinopril, captopril, Ramipril, Fosinopril, Moexipril Quinapril, Trandolapril	36 hours before Day 1 (visit 2) through end of study	discontinue study treatment
Aliskiren (only subjects with concurrent diabetes)	duration of study	discontinue study treatment
Nesiritide	duration of study	discontinue study treatment
Bile Acid sequestering agents	duration of study	discontinue study treatment

5.4.9 Emergency breaking of assigned treatment code

Not applicable.

5.5 Study completion and discontinuation

5.5.1 Study completion and post-study treatment

At the end of study visit, subjects will be asked to return all remaining study drug. The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.5.2 Discontinuation of study treatment

Subjects may voluntarily discontinue the study drug for any reason at any time.

Study drug must be discontinued under the following circumstances:

- Withdrawal of consent
- Pregnancy
- Use of prohibited concomitant medication
- Any protocol deviation that constitutes a risk to the subject
- Investigator believes that continuation of study drug may be detrimental to the subject's well-being

Study medication may be discontinued at the investigator's discretion if any of the following occur:

- Any severe suspected drug related AE
- Suspected occurrence of angioedema. A subject with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the investigator to determine if it constitutes a reason for discontinuation of study medication.
- Depending on the serum potassium, blood pressure, or eGFR, subjects may need to have their study drug dose or the dose of another concomitant medication reduced or discontinued; or, if appropriate, have potentially contributing agents adjusted. Refer to appendices for treatment guidelines for hyperkalemia, hypotension or renal dysfunction, respectively.

If discontinuation of study treatment occurs, the subject should return to the clinic as soon as possible, after discontinuation of study drug, for an end of study visit. All assessments from the final visit (Visit 10) in the visit schedule of assessments (Table 6-1) must be completed and recorded in the eCRF. The study completion eCRF will also need to be completed. The investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this information on the Study Completion eCRF.

5.5.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent (WoC) occurs only when a subject does not want to participate in the study anymore and does not want any further visits or assessments and does not want any further study related contacts and does not allow analysis of already obtained biologic material

At the time a subject withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information on the Study Completion eCRF. Study drug must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

5.5.4 Lost to follow-up

For subjects 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 subject, e.g. dates of telephone calls, registered letters, etc. A subject will not be formally considered lost to follow-up until all efforts to contact the subject have been exhausted.

5.5.5 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, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the subject must be seen as soon as possible and treated as a prematurely withdrawn subject. 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 subject's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

All assessments are listed in Table 6-1. Assessments that are to be reported in the clinical database are marked with an 'x'. Assessments that will only be reported in the source documentation are marked with an 's'. Subjects should be seen for all visits on the designated day or as close to it as possible, with an allowed visit window of ± 3 days for visits 3, 4, 5, 6 and an allowed visit window of ±7 days for visits 7, 8, 9, and 10. Eligible subjects may start study treatment once it is confirmed that they meet all inclusion criteria and none of the exclusion criteria.

Blood and urine samples for protocol required assessments will be collected and submitted to the central laboratory. Any additional routine blood tests performed per standard of care (e.g. renal function, electrolytes) will be at the discretion of the principal investigator.

Protocol required assessments for the baseline visit, including echocardiography, will be done according to the schedule of assessments (Table 6-1).

Subjects may be contacted for safety evaluations for 30 days after the last dose. Documentation of attempts to contact the subject should be recorded in the source documentation. Unscheduled visits for safety/medication evaluation/unscheduled assessments are permitted at any time during the study.

Table 6-1 Assessment schedule

Schedule of Assessments

Visit number	1	2	3	4	5	6	7	8	9	10/ EOS	**Unscheduled Visit**◊
Period	**Screening**	**Baseline**	**Titration / Maintenance**								
Day	Day -28 to Day -1	Day 1	14	30	45	60	90	180	270	365	
Inclusion/Exclusion	X	X									
Informed Consent	X										
Demographics	X										
Medical History	X										
HF Signs/Symptoms and NYHA Classification	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination	s	s		s		s	s	s	s	s	s
Limited Cardiovascular Physical examination[1]			s		s						
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Height	X										
Weight	X	X	X	X	X	X	X	X	X	X	X
Safety Laboratory (Chemistry/Hematology) [5]	X	X	X	X	X	X	X	X	X	X	X
Laboratory (per protocol) Renal function/Potassium[6,7]	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events/Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Assess for Cardiovascular Events) [11]		X	X	X	X	X	X	X	X	X	X

Schedule of Assessments

Visit number	1	2	3	4	5	6	7	8	9	10/ EOS	**Unscheduled Visit**[◊]
Period	**Screening**	**Baseline**	**Titration / Maintenance**								
Day	Day -28 to Day -1	Day 1	14	30	45	60	90	180	270	365	
Angioedema assessment		X	X	X	X	X	X	X	X	X	X
Blood for Biomarkers (all subjects)[6,7,8]		X	X	X	X	X	X	X	X	X	X
Urine for Biomarkers (all subjects) [6,8]		X	X	X	X	X	X	X	X	X	X
Labile plasma biomarkers (up to 300 subjects)[6,7,10]		X	X	X	X	X	X	X	X	X	X
Serum pregnancy test [2]		X					X	X	X	X	X
Urine Pregnancy tests [3]	X	X									X
Echocardiogram		X						X		X	X
Dipstick urinalysis[4]	X						X			X	X
KCCQ-23		X	X	X		X	X	X	X	X	X
Dispensation of medication[9]		X	X	X	X	X	X	X	X		X
Drug accountability		s	s	s	s	s	s	s	s	s	s
Dosage Administration Record		X	X	X	X	X	X	X	X		X
IRT Call	X	X	X	X	X	X	X	X	X	X	X
Screening Disposition	X										
Study completion/early termination in IRT	X	X	X	X	X	X	X	X	X	X	X

Schedule of Assessments

Visit number	1	2	3	4	5	6	7	8	9	10/ EOS	**Unscheduled Visit**◊
Period	**Screening**	**Baseline**	**Titration / Maintenance**								
Day	Day -28 to Day -1	Day 1	14	30	45	60	90	180	270	365	

* S: to be documented in the source data.

◊Unscheduled Visit Assessments marked with (x) are optional procedures that may be performed at the investigator's discretion, or if the subject withdraws early from treatment or study.

1. Limited Cardiovascular Physical Exam to be completed at Days 14 and 45 (Visits 3 and 5).
2. A serum pregnancy test is not required for a woman who is sterile or who is post-menopausal. All serum pregnancy tests will be sent to the central laboratory.
3. Urine pregnancy test will be performed on site for the visits 1 and 2.
4. Urine dipstick. If positive, send full urinalysis to central laboratory.
5. Abbreviated chemistry panel includes electrolytes and creatinine.
6. Must be strictly processed and stored according lab manual instructions and timelines.
7. Includes cardiac, renal, and drug mechanism of action biomarkers.
8. Includes urinary biomarkers such as cGMP.
9. 36-hr washout required pre-dose at visit 2 (baseline) to avoid drug-drug interaction between ACEis and NEPi.
10. Sub-study (N=up to 300) with plasma biomarkers with samples collected with blood draw at Visits 2,3,4,5,6,7, 8, 9, and 10.
11. Refer to protocol section 6.5.2 Cardiovascular Events.

6.1 Information to be collected on screening failures

All subjects who have signed informed consent but not entered into the next epoch will have the study completion page for the screening epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Rescreening

Rescreening may be allowed under certain conditions. Request from the investigator/site staff to rescreen patients will be handled on a case-by-case basis with Clinical Trial Lead approval required before proceeding with the rescreening. Rescreening cannot be done if a patient was previously enrolled in the study.

If a patient rescreens for the study, the patient must sign a new informed consent (ICF) and be issued a new patient number prior to any screening assessments being conducted under the new patient number. The date of the new informed consent signature must be entered on the Informed Consent eCRF to correspond to the new patient number.

6.3 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data to be collected on all subjects include: year of birth, age, sex, race, ethnicity and source of subject referral. Relevant medical history/current medical condition data includes data until the start of study drug. Where possible, diagnoses and not symptoms, will be recorded. HF medications and other CV medications will be recorded on eCRFs designed to facilitate separation from non-CV medications. Likewise, detailed HF history and other relevant CV medical history will be recorded on eCRFs separately from relevant non-CV medical history.

6.4 Treatment exposure and compliance

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the care giver. This information should be captured in the source document at each visit. Subject compliance should be at least 80% during the titration and maintenance treatment period. The investigator and/or study personnel will counsel the subject if compliance is below 80%. Study drug accountability will also be determined by the site monitor while performing routine site visits and at the completion of the study.

Duration of the study titration and maintenance study drug exposure will be calculated based upon the start and stop dates recorded in the Dosage Administration Record eCRF.

6.5 Efficacy

The efficacy variables are:

Primary:

- Change in concentration of NT-proBNP from baseline to one year
- Change in LVESVi, LVEDVi, LVEF, and LA volume index (LAVi) from baseline to one year

Secondary:

- Change in concentration of NT-proBNP from baseline to 6 months
- Change in LVESVi, LVEDVi, LVEF, and LA volume index (LAVi) from baseline to 6 months
- Change in KCCQ-23 baseline to one year

Exploratory:

- Change in concentration of other more stable biomarkers reflecting mechanism of action of sacubitril/valsartan and/or HF prognosis ("efficacy" biomarkers) from baseline-to-interim study visit, across one year of management, and examined as a function of change in echocardiographic variables
- Total cardiovascular events following sacubitril/valsartan initiation and up-titration, during the follow up period of 12 months. The CV events include:
  1. Worsening heart failure (WHF)
  2. Heart failure hospitalization
  3. CV death
- In a subset of subjects (N=up to 300) with collected and processed samples:
  1. Effects of sacubitril/valsartan on concentrations of BNP, as determined by several different assays used in clinical practice.
  2. Change in concentration of labile biomarkers thought to reflect the mechanism of action of sacubitril/valsartan ("MOA" biomarkers) from baseline-to-interim study visit, across one year of management, and examined as a function of change in echocardiographic variables.

6.5.1 Heart failure signs and symptoms

Signs and symptoms of heart failure will be reviewed by the investigator at all visits during the study. The signs and symptoms evaluation may include, but are not limited to, paroxysmal nocturnal dyspnea, fatigue, edema, dyspnea at rest, dyspnea upon effort, orthopnea, rales, jugular venous distention, presence of a third heart sound. NYHA classification will be assessed and scored at each visit.

6.5.2 Cardiovascular Events

Detailed information will be collected on:

- All deaths
  - CV versus non-CV
    - Sudden versus non-sudden
- Resuscitated Sudden Death
- Hospitalization for HF
- Worsening HF

Novartis' reporting guidelines for AE and SAE as outlined in Section 7.1 and Section 7.2 must be followed, independent from the circumstance that an event is also reported as a cardiovascular event.

6.5.3 Biomarkers in full subject population

Blood and urine samples for analysis of stable biomarkers related to heart failure or study drug mechanism of action will be collected in all subjects at Visits 2, 3, 4, 5, 6, 7, 8, 9 and 10 as indicated in Table 6-1. Biomarkers will be used to elucidate the effect of study drug as well as to explore drug effect and may also be used to determine event risk. Blood biomarkers may include, but are not limited to: NT-proBNP, high sensitivity Troponin, and sST2. Urine biomarkers may include, but are not limited to, cGMP. Biomarker values will be blinded to the site and the Novartis clinical study team. The list of blood and urine biomarkers may change during the course of the study as new or more relevant biomarkers related to heart failure or study drug mechanism are determined. Biomarker analysis may also occur retrospectively after study close using samples that are biobanked with biomarker decisions dependent on study outcome and/or new biomarkers relevant to heart failure or the study drug. Details of sample collection, handling and shipment will be provided to investigators in the laboratory manual.

6.5.4 Biomarkers Sub-study

Samples for labile blood biomarkers related to heart failure or study drug mechanism of action will be collected at sites having the required expertise and equipment. This sub-study is to include approximately 30% of the enrolled subjects (up to 300 subjects) with samples collected at Visits 2, 3, 4, 5, 6, 7, 8, 9, and 10. Biomarkers may include markers such as: ANP, Adrenomedullin, and proBNP1-108.

In addition, BNP samples will be collected at Visits 2, 3, 4, 5, 6, 7, 8, 9, and 10 for analysis using several different BNP assay kits that are routinely used in clinical practice.

Biomarkers will be used to elucidate the effect of study drug as well as to explore drug effect and may also be used to determine event risk. Biomarker values will be blinded to the site and the Novartis clinical study team. The list biomarkers may change during the course of the study as new or more relevant biomarkers related to heart failure or study drug mechanism are determined. Biomarker analysis may also occur retrospectively after study close using the biomarker sub-study biobank with biomarker decisions dependent on study outcome and/or new biomarkers relevant to heart failure or the study drug. Details of sample collection, handling and shipment will be provided to investigators in the laboratory manual.

6.5.5 Appropriateness of efficacy assessments

The selected efficacy variables for this study including changes in NT-proBNP and other biomarkers concentrations, as well as heart failure signs and symptoms are standard for the evaluation of therapeutic agents in a heart failure population.

6.6 Safety

- Incidence of worsening renal function, defined as an increase in serum creatinine of ≥0.5mg/dl and worsening of the eGFR by at least 25%
- Incidence of symptomatic hypotension
- Incidence of hyperkalemia (Potassium >5.5 meq/l)
- Incidence of angioedema

Safety assessments will consist of monitoring and recording of all adverse events and serious adverse events, evaluation of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations.

6.6.1 Physical examination

A complete physical exam will be performed at visit 1 (screening), visit 2 (baseline), visit 4 (Day 30), visit 6 (Day 60), 7 (Day 90), 8 (Day 180), 9 (Day 270), and 10 (Day 365). It will include the examination of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and vascular and neurological examinations. If indicated based on medical history, and/or symptoms, rectal, external genitalia, breast and pelvic exams will be performed.

Limited cardiovascular physical examination will be performed at visit 3 (Day 14) and visit 5 (Day 45), except where a complete physical examination is required (see above), and will include the examination of vital signs (systolic and diastolic blood pressure, pulse and respiration rate), heart and lung sounds, jugular venous distension, and extremities.

Signs and symptoms of heart failure will be reviewed by the investigator at all visits during the study. The signs and symptoms evaluation may include, but are not limited to, paroxysmal nocturnal dyspnea, fatigue, edema, dyspnea at rest, dyspnea upon effort, orthopnea, rales, jugular venous distention, presence of a third heart sound. NYHA classification will be assessed and scored at each visit.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that were present prior to the subject providing written informed consent for the study must be included in the Relevant Medical History/Current Medical Conditions eCRF. Significant findings made after the subject provides written informed consent for the study which meet the definition of an adverse event must be recorded on the Adverse Event eCRF.

6.6.2 Vital signs

Vital signs will be assessed at every visit. This will include blood pressure, pulse and respiration measurements. BP will be measured using a standard sphygmomanometer with an appropriate sized cuff and the non-dominant arm in the sitting position after 5 minutes of rest. Every effort should be made to use the same arm for the subject for all vital signs assessments and where possible, the same person doing the assessment.

6.6.3 Height and weight

Height in centimeters if possible, body weight to the nearest 0.1 kg without shoes will be measured at visit 1. Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at every visit.

6.6.4 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. All suspected cases of angioedema, regardless of suspected causality, must be reported. The angioedema eCRF must be completed and the Novartis Medical Monitor must be notified.

If the angioedema event meets SAE criteria, the investigator must ensure that an SAE form is completed and submitted to Novartis Drug Safety and Epidemiology. In addition, all angioedema events will be adjudicated as described in Section 8.5.1

6.6.5 Laboratory evaluations

A central laboratory will be used for all laboratory evaluations with the exception of the urine pregnancy test (hCG) performed at visit 1 (screening) and visit 2 (baseline) at the site, required to determine eligibility and analysis of all collected specimens from screening through the final visit. Details on the collections, shipment of samples and reporting of results by the central laboratory will be provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

For laboratory values that exceed the boundaries of a notable laboratory abnormality additional laboratory evaluations should be performed, as judged appropriate by the investigator. If the laboratory abnormality induces clinical signs or symptoms, or requires therapeutic intervention, then the diagnosis or medical condition must be entered on the AEs screen of the subject's eCRF. 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 subject must be followed until the abnormality resolves or until it is judged to be permanent. This investigation may include continued monitoring by repeat laboratory testing or by performing additional laboratory tests as deemed necessary by the investigator or the Novartis medical monitor.

6.6.5.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured at all visits: 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 (central lab).

6.6.5.2 Clinical chemistry

Blood urea nitrogen (BUN), glucose, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), alkaline phosphatase, sodium, potassium, chloride, calcium, hemoglobin A1C, total protein, albumin, uric acid, and lipid profile will be measured at all Visits 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 (central lab).

6.6.5.3 Urinalysis

Dipstick-test determination of specific gravity, pH, blood, total protein, bilirubin, glucose ketones, and leukocytes will be measured at Visits 1, 7 and 10 (local lab). Microscopy and

WBC and RBC sediments will also be assessed in case of an abnormal dipstick test (central lab). If dipstick is positive, a qualitative microscopic determination, including white blood cells high power field (WBCs/HPF) and red blood cells high power field (RBCs/HPF) will be performed.

6.6.6 Pregnancy and assessments of fertility

All female subjects of childbearing potential will have a urine pregnancy test (hCG) performed at Visits 1 and 2 (site). In addition, these subjects will have a serum pregnancy test performed at visits 2, 7, 8, 9 and 10 (central Lab). If any of these tests are positive, the subject must be discontinued from the study.

6.6.7 Appropriateness of safety measurements

The majority of safety assessments selected for this study are standard for this indication/subject population. They include the monitoring and recording of all adverse events and serious adverse events, evaluation of hematology, blood chemistry and urine, regular measurements of vital signs and the performance of physical examinations.

6.7 Other assessments

6.7.1 The Kansas City Cardiomyopathy Questionnaire (KCCQ-23)

The KCCQ-23 is a self-administered questionnaire and requires, on average, 4-6 minutes to complete. It contains 23 items, covering physical function, clinical symptoms, social function, self-efficacy and knowledge, and Quality of Life (QoL), each with different Likert scaling wording, including limitations, frequency, bother, change in condition, understanding, levels of enjoyment and satisfaction. A change of 5 points on the scale scores, either as a group mean difference or an intra-individual change appears to be clinically significant, based on comparisons of changes in the scale scores to clinical indicators and subject global reports of change. The KCCQ is a valid, reliable and responsive health status measure for subjects with CHF and may serve as a clinically meaningful outcome in CV clinical research, subject management and quality assessment Green et al 2000.

The HF symptoms and physical limitation domains scores show the best correlation for improvements following a CHF exacerbation Green et al 2000. Thus, one of the secondary endpoints is a clinical summary score based on the HF symptoms and physical limitation domains scores of the KCCQ. All other domains will be analyzed as exploratory endpoints, as the instruments will be administered as a whole.

The KCCQ questionnaire will be completed at Visits 2, 3, 4, 6, 7, 8, 9 and 10.

The KCCQ is available in a number of validated translations. However, subjects in whose language a validated translation of the KCCQ is not available will be exempt from completing this instrument.

6.7.2 Echocardiogram

Echocardiograms will be performed at the sites by qualified echocardiographic personnel (technicians or physicians) in accordance with standard echocardiographic clinical practice.

The baseline echocardiogram will be performed before administration of study medication. The echocardiographic examination required will be a modification of the standard echocardiographic examination, and will include the majority of standard echocardiographic views normally obtained for clinical practice, in addition to specific echocardiographic assessments designed to assess LV mass, LA volume, and diastolic function (Table 6-2).

1. LV mass index, left atrial volume index
2. Diastolic function (lateral E' velocity, E/E')
3. Systolic function (ejection fraction, S' velocity)

Table 6-2 Echocardiogram Assessments

Echocardiographic view	Images obtained
• Parasternal long axis view	• 2-D image for septal and posterior wall thickness, volume and ejection fraction measures, LA size/volume • M-Mode Images • Color flow Doppler
• Parasternal Short axis view, papillary muscle level	• 2-D images for septal and posterior wall thickness
• Apical 4-chamber View	• 2-D images for volume and ejection fraction measures, LA size/volume and RV function Color flow Doppler for assessment of mitral regurgitation • Doppler Tissue Imaging of mitral annular velocities • Mitral inflow pulsed Doppler

Echocardiograms will be recorded to digital media in DICOM format (CD, or Magneto-Optical Disc) and sent to the core laboratory for analysis. All echocardiographic measurements will be made at the core laboratory (Brigham & Women's Hospital, Boston, MA: Director Scott Solomon).

The echo data obtained during Baseline (Day 1), visit 8 (Day 180) and visit 10 (Day 365) will be sent to a core laboratory for evaluation and analysis. A detailed manual of all echo procedures will be provided to all sites.

6.7.3 Resource utilization

Not applicable.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

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

Abnormal laboratory values or test results constitute adverse events 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 subject with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- [investigational] treatment dosage increased/reduced
- [investigational] treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- non-drug therapy given
- subject hospitalized/subject's hospitalization prolonged (see Section 7.2 for definition of SAE)

- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. 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 or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the subject.

The investigator must also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- 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 (specify what this includes)
    - 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
    - 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
    - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

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

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to Annex IV, ICH-E2D Guideline).

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 subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

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

7.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days [after the last study visit/ following the last administration of study treatment if there are post-treatment follow-up visits with no required procedures] must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period [after the last study visit/ following the last administration of study treatment if there are post-treatment follow-up visits with no required procedures] should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

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

Information about all SAEs is collected and recorded on the 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 Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the subject continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (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.

7.3 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum event:
  - confirmed (after ≥24h) increase in serum creatinine of ≥25% compared to baseline during normal hydration status
- Urine event
  - new onset (≥1+) proteinuria; confirmed by doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable)
  - new onset (≥1+), hematuria or glycosuria

Every renal laboratory trigger or renal event as defined in Table 14-1 in Appendix 2 should be followed up by the investigator or designated personnel at the trial site as summarized in Appendix 2.

7.4 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, subject or consumer (EMA definition).

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) 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 a SAE

7.5 Pregnancy reporting

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

8 Data review and database management

8.1 Site monitoring

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

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the

subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the (e)CRF entries. 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 (e)CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRFs) using fully validated software that conforms to US CFR 21Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

8.3 Database management and quality control

The designated CRO staff working on behalf of Novartis will review the data entered into the CRFs by investigator staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data.

8.4 Data Monitoring Committee

Not applicable.

8.5 Angioedema Adjudication Committee

8.5.1 Composition and Purpose

The Angioedema Adjudication Committee (AAC) consists of a group of experts in clinical angioedema who have been selected according to their educational, clinical, and research experience and are independent from Novartis. The purpose of the AAC is to review and to adjudicate all suspected angioedema events in a uniform and consistent manner and to assign severity for each confirmed case for the project wide sacubitril/valsartan program. The AAC will remain blinded to treatment allocation during the adjudication process whenever possible and necessary.

8.5.2 Overview of Site Responsibility

An overview of site responsibility for reporting angioedema is described below.

At each study visit, it is important for the investigator to pay special attention to any swelling or edema that may resemble angioedema or angioedema-like events that may be reported by subjects. There will be a separate eCRF for angioedema events. If such an event occurs, the investigator will complete an Adjudication Questionnaire for an Angioedema-like Event form (provided by Novartis) to summarize the event, its treatment, and its ultimate outcome and communicate this report to Novartis as soon as possible. Follow-up reports must be communicated to Novartis as soon as new information regarding the event becomes available. All hospital records related to the event must be communicated to Novartis.

Occasionally, the investigator may be contacted by Novartis, or designee, regarding AEs that were reported on behalf of subjects that may resemble an angioedema-like event. The investigator or his/her delegated staff must complete the required report forms and supply the required medical records for such events, regardless of whether the investigator views the event in question as angioedema or not.

All angioedema reports will be forwarded to an angioedema adjudication committee by Novartis or designee for assessment.

Submission of an angioedema report is not a substitution for the submission of a SAE report. If an angioedema-like event satisfies the definition of a SAE, the investigator must submit a SAE report in addition to the Adjudication Questionnaire for an Angioedema-like Event.

Please refer to the Angioedema Adjudication Site Manual for additional details regarding the process for documenting and reporting angioedema-like events.

9 Data analysis

A designated Contract Research Organization will perform the statistical analysis.

It is planned that the data from all centers that participate in this protocol will be combined, so that an adequate number of subjects will be available for analysis.

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation

Unless otherwise specified, all statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05.

Efficacy, safety, and other data will be summarized. For continuous variables, summary statistics (mean, standard deviation, median, 25th and 75th percentiles, interquartile range, minimum, and maximum) at each time point and for change from baseline to each time point will be reported by treatment group. Discrete variables will be summarized by frequencies and percentages.

9.1 Analysis sets

The following subject sets will be used for the statistical reporting and analyses:

The Treatment Set will consist of all eligible subjects.

The Full Analysis Set (FAS) will consist of all subjects with the exception for those subjects who have not been qualified for study treatment and have not received study drug, but have been inadvertently entered into the study. Efficacy variables will be analyzed based on the FAS as the primary set.

The Safety Set (SAF) will consist of all subjects who received at least one dose of study drug. The Safety Set will be used for the analyses of safety variables.

9.2 Subject demographics and other baseline characteristics

Baseline value is defined as the last non-missing assessment prior to the first dose of study medication, unless specified otherwise in the protocol.

Summary statistics will be provided for demographics and baseline characteristics. Continuous variables will be summarized using n, mean, standard deviation, median, 25th and 75th percentiles, interquartile range, minimum, and maximum. Geometric means will be used to summarize the NT-proBNP results. Categorical variables will be summarized using frequency and percentage.

The Treatment Set and FAS will be the subject sets for the above analyses.

9.3 Treatments

The overall duration on the open-label study drug will be summarized by using mean, standard deviation, median, 25th and 75th percentiles, interquartile range, minimum, and maximum. Additionally, the number and percentage of subjects will be summarized for duration category.

Concomitant medications and significant non-drug therapies, prior to and after the start of the open-label treatment epoch will be summarized by therapeutic class, and preferred term.

The Safety Set will be used for the above analyses.

9.4 Analysis of the primary variable(s)

9.4.1 Variable(s)

- Change in concentration of NT-proBNP from baseline to one year
- Change in LVESVi, LVEDVi, LVEF, and LAVi from baseline to one year.

9.4.2 Statistical model, hypothesis, and method of analysis

Pearson's correlation coefficient and its two-sided 95% confidence interval (CI) to examine the association between change in log-transformed NT-proBNP and LVESVi, LVEDVi, LVEF, and LAVi from baseline to one year will be calculated.

Similar correlation coefficients and CIs will be calculated for the following subgroups:

- Subjects with *de novo* HF (naïve to ACE inhibitor or ARB therapy) and those with previously established HF.
- Subjects with NT-proBNP values <600 pg/mL (or 400 pg/mL if hospitalized for HF within 1 year) at the time of drug initiation, and those with higher values.

- In those not receiving the target sacubitril/valsartan dose and those achieving target dose.
- In those with an NT-proBNP concentration <1000 pg/mL at Month 12 and those with NT-proBNP ≥1000 pg/mL at the same time point.
- As a function of time from baseline to an NT-proBNP value of <1000 pg/mL for subjects with a baseline value >=1000 pg/mL (percentiles of response time).
- As a function of time spent with NT-proBNP concentration <1000 pg/mL across study visits (percentiles of response time).

The primary analysis of the primary efficacy variables will be based on the Full Analysis Set.

9.4.3 Handling of missing values/censoring/discontinuations

Missing data will not be imputed.

9.4.4 Sensitivity analyses

Pearson's correlation coefficient and its 95% confidence interval (CI) to examine the association between change in log-transformed NT-proBNP and each structural cardiac measurement from baseline to one year will be calculated using the last observation carried forward (LOCF) method.

Spearman's correlation coefficient and its 95% confidence interval (CI) to examine the association between change NT-proBNP and each structural cardiac measurement from baseline to one year will be calculated based on observed cases.

9.5 Analysis of secondary and exploratory variables

9.5.1 Secondary variables

Analyses of the secondary variables will be based on the Full Analysis Set.

The secondary efficacy variables are:

1. Change in concentration of NT-proBNP from baseline to 6 months
2. Change in LVESVi, LVEDVi, LVEF, and LAVi from baseline to 6 months
3. Change in KCCQ-23 clinical summary score from baseline to 12 months

Pearson's correlation coefficient and its two-sided 95% confidence interval (CI) to examine the association between change in log-transformed NT-proBNP and LVESVi, LVEDVi, LVEF, and LAVi from baseline to 6 months will be calculated. Similar CIs will be calculated for the following subgroups:

- Subjects with *de novo* HF (naïve to ACE inhibitor or ARB therapy) and those with previously established HF.
- Subjects with NT-proBNP values <600 pg/mL (or 400 pg/mL if hospitalized for HF within 1 year) at the time of drug initiation, and those with higher values.
- In those not receiving the target sacubitril/valsartan (LCZ696) dose and those achieving target dose.
- In those with an NT-proBNP concentration <1000 pg/mL and those with NT-proBNP ≥1000 pg/mL at the same time points.

- As a function of time from baseline to an NT-proBNP value of <1000 pg/mL for subjects with a baseline value >=1000 pg/mL (percentiles of response time).
- As a function of time spent with NT-proBNP concentration <1000 pg/mL across study visits (percentiles of response time.

An analysis of variance will be done to compare the mean change in the KCCQ-23 summary score between the groups of subjects with NT-proBNP<1000 pg/mL and NT-proBNP>=1000 pg/mL at Month 12. Because the treatments in this study are not assigned randomly, the groups may consist of subjects that are systematically different from each other with respect to their baseline covariate information, therefore propensity score adjustment will be used in the comparison of treatment groups.

9.5.2 Exploratory variables

- Change in concentration of the more stable biomarkers reflecting mechanism of action of sacubitril/valsartan and/or HF prognosis ("efficacy" biomarkers) from baseline-to-interim study visit, across one year of management, and examined as a function of change in echocardiographic variables.
- Total cardiovascular events from sacubitril/valsartan initiation through the follow up period of 12 months. The CV events include:
  a. Worsening heart failure (WHF)
  b. Heart failure hospitalization
  c. CV death

1. Pearson's correlation coefficient and its two-sided 95% confidence intervals (CI) to examine the association between change in other more stable biomarkers reflecting mechanism of action of sacubitril/valsartan and/or HF prognosis ("efficacy" biomarkers) and echocardiographic variables from baseline to one year will be calculated.
2. Pearson's correlation coefficient and its two-sided 95% confidence interval (CI) to examine the association between total number of CV events and the change from baseline in biomarkers and echocardiographic remodeling indices will be calculated.
3. The total CV event rate will be calculated for subjects achieving an NT-proBNP of < 1000 pg/mL at each time point.
4. The time to an NT-proBNP value of <1000 pg/mL ("time to response") for subjects with a baseline value >=1000 pg/mL as well as a the time spent with an NT-proBNP < 1000 pg/mL ("time in response") during a year of follow up will be calculated for subjects with and without a CV event.
5. The following will calculated at each study visit for each BNP assay:
   - Change in median concentration of each BNP assay from baseline-to-interim study visit.
   - Change in median concentration of each BNP assay from last-to-present interim visit.

These analyses will be repeated for the following subgroups:

a. Subjects with *de novo* HF, naïve to ACE inhibitor or ARB therapy.

b. Subjects with BNP values <150 pg/mL (or <100 pg/mL if hospitalized within one year) at the time of drug initiation.
c. Achieved maximum dose of sacubitril/valsartan (LCZ696).

Pearson's correlation coefficient and its two-sided 95% confidence intervals (CI) to examine the association between change from baseline in concentration of labile MOA biomarkers across one year of management and the change in echocardiographic variables will be calculated.

9.5.3 Resource utilization

Not applicable.

9.5.4 Pharmacokinetics

Not applicable.

9.5.5 DNA

Not applicable.

9.5.6 Biomarkers

See Sections 9.4 and Section 9.5 for a description of the methods used to analyze the biomarkers. Any other biomarkers collected but not specifically mentioned in Sections 9.4 or Section 9.5 will be analyzed in the same manner.

9.5.7 PK/PD

Not applicable.

9.6 Other safety variables

The safety and tolerability assessments are listed below:

- AEs and SAEs
- Sitting systolic, diastolic BP, and pulse pressure
- Heart rate
- Laboratory values

The assessment of safety will be based primarily on the frequency of adverse events, SAEs, and laboratory abnormalities. Other safety data will be summarized as appropriate.

The incidence of treatment-emergent adverse events (new or worsened) will be summarized by primary system organ class, preferred term, severity, and relationship to study drug. In addition, the incidence of death, SAEs, and AEs leading to discontinuation will be summarized separately by primary system organ class and preferred term.

Laboratory data will be summarized by presenting shift tables using extended reference ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (mean, median, standard deviation, 25th and 75th

percentiles, interquartile range, minimum and maximum) and by the flagging of notable values in data listings.

Data from other tests (e.g., ECG) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

Safety analyses will be performed based on the Safety Set. There will be no inferential analyses of the safety data.

9.7 Interim analyses

Not applicable

9.8 Sample size calculation

The objective of this study is to estimate the correlation coefficient between change in log NT-proBNP and each structural cardiac measurement overall and in each subgroup of interest. We would like to estimate the correlation coefficient with a precision (half-width of the confidence interval (CI)) of at least 0.15 for a 2-sided 95% CI in the intended subgroups of interest. The subgroups of interest are: (1) subjects with HFrEF and "low" NT-proBNP (<600 if not hospitalized or <400 if hospitalized) or "low" BNP (<150 if not hospitalized, <100 if hospitalized) at baseline (Ambrosy 2012), (2) subjects with new onset HF and/or RAAS naïve (Fonarow 2010), and (3) subjects who are not receiving the target sacubitril/valsartan dose (McMurray 2014). It is estimated that these subgroups will represent approximately 25%, 20% and 30% of the study population, respectively. Assuming, the population correlation coefficient of -0.35 (Weiner 2013) for the overall study sample and within each subgroup, the smallest sample size that would yield a precision of at least 0.15 for the estimated correlation coefficient would be n=133. Accounting for assumed 20% drop-out rate, 166 patients would be required. If the n=166 was the smallest subgroup of interest (20% of the overall study population), an overall sample size of 830 would be required to enroll in this study. For any other subgroup with more than 166 patients will yield precision smaller than 0.15 for the estimated correlation coefficient. For the overall sample size of N=830 patients the precision of the estimate of correlation coefficient would be 0.07 (PASS 2008).

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

Eligible subjects/subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of

doing so, after such consent has been provided by a legally acceptable representative(s) of the subject. In cases where the subject's representative gives consent, the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. 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 subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing 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 requirement for the duration of the study. If there is any question that the subject will not reliably comply, they must not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

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

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance (CQA), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

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

11 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 subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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.

11.1 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 intended to eliminate an apparent immediate hazard to subjects 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 subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

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13 Appendix 1: Clinically notable laboratory values

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

Hematology

RBC count	>50% increase, >20% decrease
Hemoglobin	>50% increase, >20% decrease
Hematocrit	>50% increase, >20% decrease
WBC count	>50% increase, >50% decrease
Platelet count	>75% increase, >50% decrease

Blood Chemistry

ALT (SGPT)	>150% increase
AST (SGOT)	>150% increase
BUN	>50% increase
Creatinine	>50% increase
Total bilirubin	>100% increase
Alkaline phosphatase	>100% increase
Potassium	>20% increase, >20% decrease

14 Appendix 2: Specific Renal Alert Criteria and Actions

Table 14-1 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider subject hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria ≥1+ Albumin- or Protein-creatinine ratio increase ≥2-fold Albumin-creatinine ratio (ACR) ≥30 mg/g or ≥3 mg/mmol; Protein-creatinine ratio (PCR)≥150 mg/g or >15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick glycosuria ≥1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor subject regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, 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.	

15 Appendix 3: Treatment guidelines for hyperkalemia (serum potassium greater than or equal to 5.5 mEq/L)

General principles

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

Subjects with elevated potassium value will be managed according to the corrective actions outlined below and the investigator's clinical judgment. Hyperkalemia should be followed until resolution.

Recommended corrective action for management of hyperkalemia

Serum potassium > 5.3 and less than or equal to 5.5 mEq/L

- Confirm 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, low-salt substitutes etc.)
- 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:
  - Aldosterone antagonists (if they are believed to be the most likely cause of hyperkalemia)
  - 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
- Repeat serum potassium measurement within 3 to 5 days
- If serum potassium remains > 5.3 and ≤ 5.5 mEq/L, regularly monitor serum potassium levels to ensure stability (suggested once monthly)
- Consider down-titration of study medication, according to investigator's medical judgment.

Serum potassium > 5.5 and < 6.0 mEq/L

- Confirm potassium concentration in a non-hemolyzed sample
- Consider down-titration or temporarily discontinue study drug according to investigator medical judgment.
- Apply all measures outlined for serum potassium > 5.3 and ≤ 5.5 mEq/L
- Repeat serum potassium measurement after 2-3 days
- If serum potassium < 5.5 mEq/L, consider resumption of study drug at lower dose with repeat potassium within 5 days

Serum potassium greater than or equal to 6.0 mEq/L

- Immediately discontinue study drug
- Confirm potassium concentration in a non-hemolyzed sample
- Urgently evaluate subject and treat hyperkalemia as clinically indicated
- Apply all measures outlined for serum potassium > 5.3 and < 6.0 mEq/L
- If serum potassium < 5.5 mEq/L, consider resumption of study drug at lower dose with repeat potassium within 5 days

16 Appendix 4: Guidelines for the management of blood pressure

Guidelines:

1. Investigator should monitor blood pressure closely
2. If symptomatic hypotension occurs:
    a. Correct any treatable cause, e.g. hypovolemia
    b. If hypotension persists, any antihypertensive drug and non-disease-modifying drugs, such as diuretics, CCBs, nitrates, and α-blockers, should be down-titrated or stopped first before down-titration of the study drug is considered
3. If hypotension persists, the study drug should be down-titrated or even temporarily withdrawn. The dose re-challenge and medication adjustment guidelines described in Section 5.4.5 should be adhered to as much as possible.

17 Appendix 5: Guidelines for the management of renal dysfunction

General principles:

Glomerular filtration rate in HF subjects depends on intrinsic renal function and on a balance between afferent and efferent glomerular arterial tonicity. This tonicity is partly regulated by a stimulation of angiotensin II and could be affected by either study medication. Moreover, renal dysfunction may develop or may deteriorate in some subjects after study drug administration. These recommendations have been developed to guide the investigators in managing subjects with renal dysfunction after administration of study drug.

Two types of response to serum creatinine increase are described:

Surveillance situation

If, at any time after study drug administration, eGFR decreases by ≥ 25% from baseline (or if serum creatinine concentration increase to 2.5 mg/dL [221 µmol/L]), the investigator will check for potentially reversible causes of renal dysfunction such as:

- Non-steroidal anti-inflammatory drug intake, antibiotics, or other treatments known to affect creatininemia
- Volume decrease, including that resulting from excessive dosing of diuretics
- Urinary infection
- Urinary tract obstruction
- Study medication

Action situation

If a subject eGFR decreases by ≥ 40% from baseline (or if serum creatinine concentration rises above 3 mg/dL (265 µmol/L), the investigator will check for potentially reversible causes of renal dysfunction (see above).

If the investigator judges that study medication has to be stopped, he/she will have to contact the Novartis medical monitor or his/her designee. Thereafter, serum creatinine assessments will have to be repeated at least each week until levels return to acceptable values. If study medication was stopped, every effort will be done to restart it again, according to clinical conditions.

18 Appendix 6: Kansas City Cardiomyopathy Questionnaire

The KC Cardiomyopathy Questionnaire

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Showering/Bathing	☐	☐	☐	☐	☐	☐
Walking 1 block on level ground	☐	☐	☐	☐	☐	☐
Doing yardwork, housework or carrying groceries	☐	☐	☐	☐	☐	☐
Climbing a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Hurrying or jogging (as if to catch a bus)	☐	☐	☐	☐	☐	☐

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** have become…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
☐	☐	☐	☐	☐	☐

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
☐	☐	☐	☐	☐	☐

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
☐	☐	☐	☐	☐	☐

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
☐	☐	☐	☐	☐	☐

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
☐	☐	☐	☐	☐

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
☐	☐	☐	☐	☐

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
☐	☐	☐	☐	☐

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I felt that way **all of the time**	I felt that way **most of the time**	I **occasionally** felt that way	I **rarely** felt that way	I **never** felt that way
☐	☐	☐	☐	☐

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please place an **X** in one box on each line

Activity	**Severely** limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	☐	☐	☐	☐	☐	☐
Working or doing household chores	☐	☐	☐	☐	☐	☐
Visiting family or friends out of your home	☐	☐	☐	☐	☐	☐
Intimate relationships with loved ones	☐	☐	☐	☐	☐	☐