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Global Clinical Development - General Medicine

LCZ696

Clinical Trial Protocol CLCZ696B3301 / NCT02900378

A multi-center, prospective, randomized, double-blind study to assess the impact of sacubitril/valsartan vs. enalapril on daily physical activity using a wrist worn actigraphy device in adult chronic heart failure patients

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List of abbreviations

6MWT	6 Minute Walking Test
ACEI	Angiotensin Converting Enzyme Inhibitor
ACR	Albumin-Creatinine Ratio
AE	Adverse Event
ALP	Alkaline Phosphatase Level test
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
ARB	Angiotensin II Receptor Blocker
ARNI	Angiotensin Receptor-Neprilysin Inhibitor
AST	Aspartate Aminotransferase
AUC	Area Under Curve
bid	Bis in die (twice a day)
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
CCB	Calcium Channel Blocker
CFR	US Code of Federal Regulations
COPD	Chronic Obstructive Pulmonary Disease
CHF	Chronic Heart Failure
CRF	Case Report/Record Form (paper or electronic)
CRT	Cardiac Resynchronization Therapy
CRT-P	Cardiac Resynchronization Therapy Pacemaker
CRT-D	Cardiac Resynchronization Therapy Defibrillator
COX-2	Cyclo-Oxygenase-2
CPO	Country Pharma Organization
CQA	Compliance Quality Assurance
CRO	Contract Research Organization
CT	Computed Tomography
CTC	Common Terminology Criteria
CV	Cardiovascular
DAR	Dose Administration Record
DS&E	Drug Safety & Epidemiology
DSM	Drug Supply Management
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
[redacted]	[redacted]
ESC	European Society of Cardiology
FAS	Full Analysis Set

[redacted]

GCP	Good Clinical Practice
hCG	human Chorionic Gonadotropin
HDPE	High-Density Polyethylene
HF	Heart Failure
HFmrEF	Heart Failure with mid-range Ejection Fraction
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
IB	Investigator's Brochure
ICD	Implantable Cardioverter Defibrillator
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMPs	Investigational Medicinal Products
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
i.v.	Intravenous
IVRS/IWRS	Interactive Web and Voice Response System
KCCQ	Kansas City Cardiomyopathy Questionnaire
LCZ696	Sacubitril/valsartan
LFT	Liver Function Test
LOCF	Last-observation-carried-forward principle
LVEF	Left Ventricular Ejection Fraction
MCS-12	Mental Health Composite Score
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
METs	Metabolic Equivalents
MI	Multiple Imputation
MLHFQ	Minnesota Living with Heart Failure
MRA	Mineralocorticoid Receptor Antagonist
MRI	Magnetic Resonance Imaging
MUGA	Multiple-Gated Acquisition scan
M6min	Maximum six minutes of daily activity (6-minute walk test)
NEP	Neprilysin
NSAID	Non-Steroidal Anti-Inflammatory Drug
NT-proBNP	N-terminal prohormone of Brain Natriuretic Peptide
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PCR	Protein-Creatinine Ratio
PCS-12	Physical Health Composite Score

[redacted]

PGA	Patient Global Assessment
[redacted]	[redacted]
p.o.	Per os (oral)
PK/PD	Pharmacokinetic/Pharmacodynamic
PP	Per-Protocol
[redacted]	[redacted]
PT/INR	Prothrombin Time/International Normalized Ratio
QM	Quality Management
QoL	Quality of Life
RAAS	Renin Angiotensin Aldosterone System
SAE	Serious Adverse Event
SAF	Safety Data Set
SBP	Systolic Blood Pressure
SD	Standard deviation
[redacted]	[redacted]
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total Bilirubin Level
TD	Study Treatment Discontinuation
ULN	Upper Limit of Normal
UNS	Unscheduled visit
VAD	Ventricular Assistance Device
VAS	Visual analog scale
WHO	World Health Organization
WoC	Withdrawal of Consent
yGT	Gamma Glutamyl Transferase

[redacted]

Glossary of terms

Cohort	A specific group of patients/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 patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient 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	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 patients/subjects with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient 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 patient 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 patient 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

[redacted]

Amendment 4

Amendment rationale

This amendment is introduced as a consequence of new and previously unavailable key data regarding the use of accelerometry as a clinical endpoint in trials concerning heart failure patients and new positioning from the Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency on the use of 6 min walk test (6MWT) in heart failure studies (CHMP, 2017).

When conceptualizing this study, there was a paucity of data validating actigraphy and especially actigraphy as measured by the MotionWatch8, in heart failure patients. However, access to the first interpretable results of another recently completed study, the AWAKE-HF trial (NCT02970669), has raised doubts to whether accelerometry is the best available and sensitive enough method to measure potential change in daily physical activity in heart failure patients. This is in line with recent literature from use of accelerometry in other related disease areas such as in COPD. A recent study (Troosters et al., 2018) demonstrated that a specific investigational pharmacotherapy in COPD combined with self-management behavior-modification program (SMBM) showed statistical and clinical improvement in 6MWT compared to a comparator drug and SMBM. However, this observed improvement in 6MWT did not translate into increased daily physical activity as measured by an actigraphy device.

The 6MWT is a commonly used method to clinically assess the patient's physical activity in cardiopulmonary diseases and is a validated endpoint in heart failure studies as such (Ferreira et al., 2016). Combined with the fact that the 6MWT is positioned by the CHMP to be a reliable and preferred method for elucidating functional capacity, whereas accelerometry is still not validated in heart failure, we have increased the importance of the 6MWT in this current study from a secondary endpoint to now a co-primary endpoint. As the 6MWT was already accounted for when calculating the initial sample size when planning the study, the changes implemented herein do not affect the study sample size nor the remaining of the trial conduct .

Study status

The study is fully recruited and has achieved last patient last visit. The amendment does not imply changes in the study sample size.

Changes to the protocol

Section 1.2

Included 6MWT into the purpose of the trial.

Section 2

Description of the 6MWT conduct and definition of the new 6MWT related endpoints.

Section 9.1

Revision of the analysis sets due to the impact of introducing a new primary endpoint.

Section 9.4.1

[redacted]

Defining the primary study variables by including 6MWT.

Section 9.4.2

Including the definition of the primary hypothesis by adding the 6MWT variable.

Section 9.4.3

Specification of the sensitivity analysis.

Section 9.5.1

Increased the specifications of the efficacy variables.

Section 9.8

Included the testing strategy as well as a table of the power calculation of the two primary endpoints.

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

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes herein do NOT affect the trial specific model ICF.

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

Amendment 3

Amendment rationale

This amendment was introduced as a consequence to the realization that combining specific visit windows could allow a mismatch in number of days between visits and number of available study drug. In addition, we have added a precision to the dosing level ranges to avoid any ambiguity and lastly, an additional method for imputing missing data has been added.

Implementation of this amendment will secure that the study patients will have sufficient study drug throughout the study regardless of how their study visits are constructed within the new visit windows given. Additionally, adding a new method for imputing the missing data would allow better utilization of data which is not complete but useful. We do not expect, by implementing this amendment, that the study objectives or the expected overall interpretation of the results will be significantly altered.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes herein do NOT affect the trial specific model ICF.

[redacted]

Amendment 2

Amendment rationale

This amendment was introduced due to a specific requirement from Health Authorities. The scope of this amendment is to change specific criteria for when patients are found to be eligible for re-screening in this study.

Implementation of this amendment will increase the precision of patients re-screened and optimize the recruitment of the patients of interest of this study. We do not expect, by implementing this amendment, that the study objectives or the expected overall interpretation of the results will be significantly altered. The requirements by the Health Authorities are found to be well justified and therefore implemented.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes herein do NOT affect the trial specific model ICF.

Study status

The study has been submitted to Health Authorities as its first submission. So far, the trial has not yet started.

Section 6.1

Specific criteria are deleted from the definition of which patients that are eligible for re-screening in the study.

Amendment 1

This amendment was introduced as a consequence of feedback and specific requirements from Health Authorities. In summary, these requirements are put in place to detail the potential risk of interaction between specific antidiabetic medication and both the comparator and investigational medicinal product. Furthermore, a precision of specific exclusion criteria are given (26 and 32), by which prohibited concomitant medication and the need for ECG is further specified. In addition, patients eligible for re-screening in the study are further specified as well as further guidance is provided for the eligibility and potential use of the unscheduled visits between set visits. The alert criteria to kidney function are refined in appendix 3 where the Urine Events are deleted due to redundancy with Serum Events as well as appendix 6. A precision is also added in the hypothetical terms where the study might be terminated.

[redacted]

Protocol summary

Protocol number	CLCZ696B3301
Title	A multi-center, prospective, randomized, double-blind study to assess the impact of sacubitril/valsartan vs. enalapril on daily physical activity using a wrist worn actigraphy device in adult chronic heart failure patients
Brief title	randOmized stUdy using accelerometry to compare Sacubitril/valsarTan and Enalapril in Patients with Heart Failure (OUTSTEP-HF)
Sponsor and Clinical Phase	Novartis, Clinical phase IIIB
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Limitations of daily physical and social activities are common hallmark of the different physical and emotional symptoms patients with chronic heart failure (HF) experience and are often the main reason for these patients seeking medical care. When asking HF patients how they define quality of life (QoL), the ability to perform desired physical and social activities in order to meet their and their families' needs is among the most frequent definitions. An increase of physical activity in HF patients is positively correlated with improved outcome and negatively correlated with the occurrence of fatigue (as a limiting factor of physical activity) which is a known independent long-term prognostic factor. Many of the current evidence based therapies for chronic HF, such as angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) or cardiac resynchronization therapy (CRT) lead to improvement in exercise capacity. Sacubitril/valsartan is a first-in-class angiotensin receptor-neprilysin inhibitor (ARNI). It has been recently approved for the treatment of HF with reduced ejection fraction (HFrEF) by demonstrating its superiority over the ACEI enalapril in terms of mortality and morbidity in the pivotal PARADIGM-HF trial. However, while the positive effects of ACEI, ARB and CRT on exercise capacity have been widely studied, it is unknown whether sacubitril/valsartan exerts similar effects on physical activity. The purpose of this randomized, actively controlled, double-blind study with prospective data collection is to assess differences between sacubitril/valsartan versus enalapril in increasing exercise capacity and non-sedentary physical activity in HFrEF patients. Physical activity will be assessed by the 6 minute walk test, and daily physical activity will be continuously measured by means of a wrist-worn accelerometry device from 2 weeks before until 12 weeks after start of study therapy (sacubitril/valsartan or enalapril).
Primary Objectives	• To elucidate the change in physical activity as assessed by the distance walked in meters during the 6-minute walk test between baseline and 12 weeks of study drug treatment in sacubitril/valsartan vs. enalapril patients. • To assess changes in daily non-sedentary daytime activity between baseline and after 12 weeks of treatment in sacubitril/valsartan vs. enalapril treated patients.

[redacted]

Secondary Objectives	• To compare the proportion of patients with improved performance (≥ 30m (Shoemaker et al., 2013, Tager et al., 2014) in the 6-minute walk test between sacubitril/valsartan vs. enalapril during the treatment period (weeks 0 to 12). • To demonstrate that sacubitril/valsartan is superior in improving exercise capacity as assessed by the six-minute walk test (6MWT) at week 12 in a subset of patients with baseline six-minute walk distance equal to or less than 300 meters • To demonstrate that sacubitril/valsartan is superior in improving exercise capacity as assessed by the six-minute walk test (6MWT) at week 12 in the patients with baseline six-minute walk distance between 100-450 meters. • To compare the effects of sacubitril/valsartan vs. enalapril on patients' symptom progression by means of the Patient Global Assessment (PGA) questionnaire at week 4, week 8 and week 12. • To assess dynamics of changes from baseline in daily non-sedentary daytime physical activity in sacubitril/valsartan vs. enalapril treated patients in weekly and two-weekly intervals • To assess changes from baseline in mean daily non-sedentary daytime physical activity classified by its intensity for sacubitril/valsartan vs. enalapril treated patients after week 4, week 8 and week12. • To assess the difference in non-sedentary daytime physical activity between sacubitril/valsartan vs. enalapril treated patients during the treatment period (weeks 0 to 12). • To assess changes from baseline on M6min (an actigraphy-based measure of the peak six minutes of daytime physical activity) in sacubitril/valsartan vs. enalapril treated patients after week 4; week 8 and week 12. • To assess changes from baseline (week 0) in exercise capacity assessed by means of the 6-minute walking test at weeks 4, 8 and 12.
Study design	This is an European, randomized, actively controlled, double-blind, double-dummy, interventional study with prospective data collection powered to assess differences between sacubitril/valsartan versus enalapril in terms of increasing daily physical activity in HFrEF patients. The study comprises 6 visits over 14 weeks. Actigraphy will be performed during the entire duration of the study by means of a wrist-worn accelerometry device. The device will be worn continuously for two weeks prior to randomization in order to obtain an individual baseline for each patient, and throughout the double-blind treatment period of the study (12 weeks).
Population	Adult male and female patients with symptomatic HFrEF managed in an ambulatory or outpatient setting (i.e. primary care physicians, office based cardiologists, HF outpatient clinics). Patients will be randomized in a 1:1 allocation to receive sacubitril/valsartan or enalapril during the double-blind treatment period. The target projected sample size is 600 patients (300 patients per treatment arm) included at approximately 140 study sites across Europe.
Key Inclusion criteria	• Written informed consent obtained before any study assessment is performed. • Ambulatory ≥ 18 years of age with a diagnosis of chronic symptomatic

[redacted]

	HF (NYHA class ≥ II) with reduced ejection fraction, defined as known LVEF ≤ 40% (known LVEF ≤ 40% at Visit 1 reflects any local measurement, made within the past 12 months using echocardiography, MUGA, CT scanning, MRI or ventricular angiography, provided no subsequent measurement with LVEF results above 40% is available). **AND** one of the following two criteria: - Plasma NT-proBNP level of ≥ 300 pg/mL or BNP ≥ 100 pg/mL (measurement may be recorded no longer than past 12 months) **OR** - Confirmation of a heart failure hospitalization last 12 months. • Patients must be on stable HF medication (ACEI/ARB, beta-blockers and MRA) for at least 4 weeks prior to Visit 1, where the minimal daily dose of ACEI/ARB dose is equivalent to at least 2.5 mg/d enalapril (See Table 3-1). • Willingness to wear the accelerometer wristband continuously for the duration of the trial. • Patients must be living in a setting, allowing them to move about freely and where they are primarily self-responsible for scheduling their sleep and daily activities.
Key Exclusion criteria	• History of hypersensitivity to any of the study drugs or their excipients or to drugs of similar chemical classes • Use of sacubitril/valsartan prior to Visit 1. • Bedridden patients, or patients with significantly impaired/limited physical activity and/or fatigue due to medical conditions other than HF, such as, but not limited to angina (chest pain at exertion), arthritis, gout, peripheral artery occlusive disease, obstructive or restrictive lung disease, malignant disease, neurological disorders (e.g. Parkinson's or Alzheimer's disease, central and peripheral neuroinflammatory and -degenerative disorders or functional central nervous lesions due to hemodynamic or traumatic incidents), injuries (incl. diabetic foot ulcers) or missing limbs • Patients with palsy, tremor or rigor affecting the non-dominant arm. • Patients with any skin or other condition of the non-dominant arm that would limit the ability to wear the actigraphy device continuously (24h/day) over 14 weeks. • Patients fully depending on a mobility support system, e.g. wheelchair, scooter or walker. Patients are allowed to use a cane as long as this is not used with the non-dominant arm.
Study treatment	• Sacubitril/valsartan (target dose 97 mg/103 mg bid) • Placebo to match sacubitril/valsartan at all dose levels • Enalapril (target dose 10 mg bid) • Placebo to match enalapril at all dose levels
Efficacy assessments	• Actigraphy-derived parameters • 6-minute walking test • Patient Global Assessment questionnaire (PGA) [redacted]

[redacted]

	[redacted]
Key safety assessments	• Adverse event monitoring • Physical examinations and blood pressure monitoring • Monitoring of laboratory markers in blood (e.g. potassium, creatinine, AST/ALT).
Other assessments	Not applicable
Data analysis	Descriptive statistical analysis will be provided for all data assessed in this study: Quantitative data (e.g. age) will be described by the statistical parameters valid N, missing N, mean, standard deviation (SD), minimum, median, and maximum. If indicated by the data, an additional frequency distribution will be provided after appropriate grouping of data. Qualitative (e.g. gender) and categorical variables (e.g. score values) will be presented by absolute and relative frequency distributions. The primary endpoint will be tested between enalapril and sacubitril/valsartan using analysis of covariance (ANCOVA), with the baseline value as a covariate. Two-sided tests of significance (with $\alpha = 0.05$) between the two treatment groups will be performed for all secondary endpoints on an exploratory basis, using appropriate testing procedures. All analyses will be carried out by means of the SAS® software package (version 9.2 or higher).
Key words	Physical activity, actigraphy, sleep, sacubitril/valsartan, enalapril, heart failure, reduced ejection fraction, randomized controlled trial, accelerometry

[redacted]

1 Introduction

1.1 Background

Heart failure (HF) is one of the main causes for hospitalization and pharmacotherapy use in the western world; in Europe its prevalence varies between 1-2%, but rises to more than 10% for people older than 70 years (Mosterd and Hoes, 2007). HF is defined as an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate that commensurate with the requirements of the metabolizing tissues (Ponikowski et al., 2016). The typical symptoms of chronic HF initially bringing patients to medical attention include breathlessness, ankle swelling, fatigue and reduced exercise tolerance. Based on left ventricular ejection fraction (LVEF), HF can be classified as HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF) or HF with mid-range ejection fraction (HFmrEF) (Ponikowski et al., 2016). Thus, LVEF in HF patients is important, both as a prognostic marker (lower LVEF is associated with worse prognosis (Curtis et al., 2003) and for guiding therapeutic decisions (Ponikowski et al., 2016).

HF patients have a grim prognosis; the five-year survival rate is about 50% (Mozaffarian et al., 2015) and the mortality in patients suffering from severe heart failure is reported to be around 50% within one year (Friedrich and Bohm, 2007). In addition, due to the chronic progressive nature of HF, increasing symptom burden (e.g. progression of breathlessness, fatigue, edema etc.) has a negative impact on multidimensional domains of the patients' daily health related quality of life (QoL), especially related to physical, mental, emotional and social functioning (Ponikowski et al., 2016). Poor QoL in HF patients is associated to higher hospitalization and mortality rates (Alla et al., 2002, Konstam et al., 1996, Moser et al., 2009). In fact, HFrEF patients report much stronger deterioration of their QoL as compared to patients with other chronic illnesses such as chronic lung disease, arthritis, diabetes, hypertension or angina (Hobbs et al., 2002, Stewart et al., 1989). There is also evidence that amongst symptomatic HF patients, clinically meaningful improvements of QoL are considered to be the most important outcome measure (Stanek et al., 2000), thus underlining its increasing relevance as a treatment goal in HF management (Moser et al., 2009).

Limitations of daily physical and social activities are a common hallmark of the different physical and emotional symptoms patients with chronic HF experience (Heo et al., 2009, Wilson et al., 1999) and thus are often the reason for these patients to seek medical care (Pina et al., 2003). This is also reflected by the increasing recognition of both physical and social activity as important domains of QoL, e.g. within standardized and validated instruments such as the Kansas City Cardiomyopathy Questionnaire (KCCQ) (Green et al., 2000) and Minnesota Living with Heart Failure Questionnaire (MLHFQ) (Rector and Cohn, 1992). When asking HF patients how they define QoL, the ability to perform desired physical and social activities in order to meet their and their families' needs was among the three definitions rated as most important (Heo et al., 2009). Medical tests utilizing physical exercise are also becoming standard examinations in HF patients as they allow an objective evaluation of exercise capacity and exertional symptoms, such as breathlessness and fatigue (Arena et al., 2011).

[redacted]

An increase of physical activity in HF patients is positively correlated with improved outcome (Arslan et al., 2007, Passantino et al., 2006, Swank et al., 2012) and is negatively correlated with the occurrence of physical fatigue, a limiting factor of physical activity and is a known independent long-term prognostic factor (Ekman et al., 2005, Walke et al., 2007). Many of the current evidence based therapies for chronic HF, such as angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) or cardiac resynchronization therapy (CRT) lead to improvement in exercise capacity (Coats, 2002, Garg and Yusuf, 1995, Ponikowski et al., 2016).

Sacubitril/valsartan is a first-in-class angiotensin receptor-neprilysin inhibitor (ARNI). It has been recently approved by the EMA for the treatment of HFrEF by demonstrating its superiority over the ACEI enalapril in terms of mortality and morbidity in the pivotal PARADIGM-HF trial (McMurray et al., 2014). In the same study, patients receiving sacubitril/valsartan after 8 months of treatment reported significantly less deterioration of their QoL (assessed by means of the KCCQ), compared to patients receiving enalapril. Despite this statistically significant difference, one might argue that PARADIGM-HF had intrinsic limitations in terms of design which likely led to underestimation of the true differences in KCCQ scores and, thus, did not allow a proper assessment of the effects of the two treatments on QoL. The baseline KCCQ score was measured at randomization, which took place after a 6-8 week long run-in period during which the patients first received target doses of enalapril and then sacubitril/valsartan. Therefore no "true" baseline QoL was captured. Due to this, especially the early effects of the respective treatments were likely not adequately captured in the PARADIGM-HF trial.

While the positive effects of ACEI, ARB and CRT on exercise capacity have been widely studied (Coats, 2002, Garg and Yusuf, 1995, Ponikowski et al., 2016), it is unknown whether sacubitril/valsartan exerts similar effects on physical activity. However, since sacubitril/valsartan did have a significant beneficial effect on the KCCQ (McMurray et al., 2014) and physical and social activity are major determinants of the KCCQ-assessed QoL, it is justified to assume that sacubitril/valsartan might increase physical activity in chronic HF patients. As described above, increasing physical activity and exercise capacity in HF patients is an important therapy goal due to its relevance for the patients' QoL and prognosis and it has been demonstrated that even a 10-minute increase in physical activity in HF patients has beneficial effects on mortality and hospitalization risk (Conraads et al., 2014). Therefore, proving a significant difference of sacubitril/valsartan in terms of improving the physical activity of chronic HF patients versus enalapril would be of clinical significance.

Assessing physical activity can be done by a plethora of methods. However, commonly used methods like patient reported physical activity questionnaires or diaries/logs are subject to personal bias and may not necessarily reflect the full effects of a therapy on a patient's daily physical activity. Intermittent supervised exercise tests (such as the frequently used 6-minute walking test or various treadmill tests) are often employed, but such supervised tests performed in a clinical setting at specific time points may not necessarily give insights into a patient's functional performance over longer periods of time (Howell et al., 2010). Lately, much attention has therefore been drawn to wearable devices which measure physical activity (Strath et al., 2013). These accelerometers provide objective and continuous assessment of physical activity during patients' daily life over long periods of time and therefore may reflect

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the true effect of a therapy on physical activity more accurately than the aforementioned methods (Gorman et al., 2014). Since medical graded activity tracking devices are small, light-weight, water resistant and have a comparably long battery life, they can be readily adopted by patients. In a 9-month prospective study in older HF patients, Howell and co-workers demonstrated a strong compliance of patients with continuously wearing the activity trackers as the study showed that 90% of the patients wore the accelerometers throughout the study (Howell et al., 2010). Importantly, in the same study, accelerometer derived functional data reflecting physical capacity showed good correlation with the traditional 6-minute walking test, as well as significant associations with subsequent events independently of age, gender, ejection fraction, NYHA class, biomarkers and baseline-6-minute walking test (Howell et al., 2010). In a similar study, Maurer and co-workers showed by means of continuous accelerometry based tracking of physical activity over 3 months in HF patients (NYHA classes I to III) that as many as 39% of patients fulfilled the criteria for anergia, a criterion-based syndrome reflecting a lack of energy. The same study showed that anergia was significantly associated with intercurrent hospitalizations (Maurer et al., 2009).

Furthermore, da Silva and colleagues demonstrated, in a small population of HF patients wearing accelerometers for six days, that they barely engage in any kind of meaningful physical activity and spend the majority of their time in sedentary or engaging only light intensity activity such as standing or slow walking (da Silva et al., 2013). This is also supported by Dontje and co-workers who found that fifty percent of the HF patients studied had a lifestyle that qualifies as sedentary (Dontje et al., 2014).

To our knowledge, no study thus far has used state of the art accelerometry technology in a big European population of HFrEF patients to compare the effects of pharmacotherapies on physical activity.

1.2 Purpose

The purpose of this randomized, actively controlled, double-blind study with prospective data collection is to assess differences between sacubitril/valsartan versus enalapril in distance walked in a 6 minute walk test (6MWT) and increasing non-sedentary daytime physical activity in HFrEF patients. To this end, the 6MWT will be performed before the patients are randomized to any of the treatments and at 12 weeks of randomized treatment whereas physical activity will be continuously measured by means of a wrist-worn accelerometry device from 2 weeks before until 12 weeks after start of study therapy (sacubitril/valsartan or enalapril).

2 Study objectives and endpoints

The main aim of the study is to elucidate any potential change in the 6MWT as assessed in the distance walked before treatment randomization compared to the end of study in both sacubitril/valsartan and enalapril treated patients and to assess differences between sacubitril/valsartan versus enalapril in improving non-sedentary daytime physical activity in HFrEF patients. The study objectives and the related endpoints are presented in Table 2-1. Patients will be performing the 6MWT at visit 2, 4, 5 and 6 and will be wearing wrist-worn accelerometry devices over the time period between two weeks prior to (baseline) and 12

weeks after randomization to receive either sacubitril/valsartan or enalapril. For each patient, an individual baseline activity level will be recorded over the two weeks prior to randomization.

Table 2-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To assess changes from baseline (week 0) in exercise capacity assessed by means of the 6-minute walking test at week 12	**Title**: Change from baseline in 6-minute walking test **Units of measure**: descriptive statistics for quantitative data, absolute and relative frequency distributions including 95% confidence intervals. **Time frame**: baseline (week 0, at randomization) and week 12	Section 9.4
To assess changes in daily non-sedentary daytime activity between baseline and after 12 weeks of treatment in sacubitril/valsartan vs. enalapril treated patients.	**Title**: Change in mean daily non-sedentary daytime activity between baseline[1] and end of study. **Description**: non-sedentary physical activity is defined as ≥178.50 activity counts per minute; the average number of minutes per day spent in non-sedentary physical activity will be calculated over 14 days before randomization (baseline[1]) and the last 14 days of treatment (i.e. week 10 to week 12). **Units of measure**: descriptive statistics for quantitative data, absolute and relative frequency distributions including 95% confidence intervals. **Time frame**: baseline[1] epoch (i.e. week -2 to week 0), end of study[2] epoch (i.e. week 10 to week 12)	Section 9.4
Secondary		
To assess changes from baseline (week 0) in exercise capacity assessed by means of the 6-minute walking test at week 12	**Title**: Proportion of patients with improved performance (≥ 30m) (Tager et al., 2014, Shoemaker et al., 2013) in the 6-minute walking test. **Units of measure**: descriptive statistics for quantitative data, absolute and relative frequency distributions including 95% confidence intervals. **Time frame**: baseline (week 0, at randomization) and week 12	Section 9.5
To demonstrate that sacubitril/valsartan is superior in improving exercise capacity as assessed by the six-minute walk test (6MWT) at week 12 in a subset of patients with baseline six-minute walk distance	**Title**: Proportion of patients with improved performance (≥ 30m) (Shoemaker et al., 2013, Tager et al., 2014) in the 6-minute walking test and which walked equal to or less than 300	Section 9.5

[redacted]

Objective	Endpoint	Analysis
equal to or less than 300 meters	meters at baseline **Units of measure**: descriptive statistics for quantitative data, absolute and relative frequency distributions including 95% confidence intervals. **Time frame**: baseline (week 0, at randomization) and week 12	
To demonstrate that sacubitril/valsartan is superior in improving exercise capacity as assessed by the six-minute walk test (6MWT) at week 12 in the patients with baseline six-minute walk distance between 100-450 meters.	**Title**: Proportion of patients with improved performance (≥ 30m) (Shoemaker et al., 2013, Tager et al., 2014) in the 6-minute walking test and which walked 100-450 meters at baseline **Units of measure**: descriptive statistics for quantitative data, absolute and relative frequency distributions including 95% confidence intervals. **Time frame**: baseline (week 0, at randomization) and week 12	Section 9.5
To assess changes from baseline (week 0) in exercise capacity assessed by means of the 6-minute walking test at weeks 4, 8 and 12	**Title**: Change from baseline in 6-minute walking test **Units of measure**: descriptive statistics for quantitative data, absolute and relative frequency distributions including 95% confidence intervals. **Time frame**: baseline (week 0, at randomization), under treatment (week 4, week 8, week 12)	Section 9.5
To assess changes in daily non-sedentary daytime activity between baseline and after 12 weeks of treatment in sacubitril/valsartan vs. enalapril treated patients.	**Title**: Proportion of patients who show increased levels (≥ 10% increase) of non-sedentary daytime physical activity at week 12 compared to baseline **Description**: non-sedentary physical activity is defined as ≥178.50 activity counts per minute; the average number of minutes per day spent in non-sedentary physical activity will be calculated over 14 days before randomization (baseline[1]) and the last 14 days of treatment (i.e. week 10 to week 12). **Units of measure**: descriptive statistics for quantitative data, absolute and relative frequency distributions including 95% confidence intervals. **Time frame**: baseline[1] epoch (i.e. week -2 to week 0), end of study[2] epoch (i.e. week 10 to week 12)	Section 9.5

[redacted]

Objective	Endpoint	Analysis
To compare the effects of sacubitril/valsartan vs. enalapril on patients' symptom progression by means of the Patient Global Assessment (PGA) questionnaire at week 4, week 8 and week 12.	**Title**: PGA score at week 4, week 8 and week 12. **Title**: Proportion of patients with improved symptoms of HF as assessed by PGA. **Description**: PGA score of symptoms of HF will be assessed as previously described. **Units of measure**: descriptive statistics for quantitative data, absolute and relative frequency distributions including 95% confidence intervals. **Time frame**: week 4, week 8, week 12	Section 9.5
To assess dynamics of changes from baseline[1] in daily non-sedentary daytime physical activity in sacubitril/valsartan vs. enalapril treated patients in weekly and two-weekly intervals.	**Title**: Change from baseline[1] in mean daily non-sedentary daytime activity in weekly and two-weekly intervals **Title**: Proportion of patients at weekly and two-weekly intervals who show increased levels (≥ 10% increase) of mean daily non-sedentary daytime physical activity compared to baseline **Description**: mean daily non-sedentary daytime physical activity (definition see above) will be calculated over weekly and two-weekly epochs and compared to baseline ([1] for two-weekly intervals). For comparison of weekly intervals, the last 7 days of baseline recording prior to randomization will serve as baseline. While two-weekly intervals allow for more stable baseline and post-titration values, weekly intervals will be used to visualize and analyze the dynamics of change post randomization. **Units of measure**: descriptive statistics for quantitative data, absolute and relative frequency distributions including 95% confidence intervals. **Time frame**: baseline[1] epoch (i.e. week -2 to week 0 for two-weekly intervals or last 7 days prior to randomization for comparison of weekly intervals), weekly or two-weekly from week 0 to week 12.	Section 9.5
To assess changes from baseline [1] in mean daily non-sedentary daytime physical activity classified by its intensity for sacubitril/valsartan vs. enalapril treated patients after week 4, week 8 and week12.	**Title**: Change from baseline[1] in mean daily light and moderate-to-vigorous non-sedentary daytime physical activity between baseline[1] and different time points under treatment. **Description**: non-sedentary physical	Section 9.5

[redacted]

Objective	Endpoint	Analysis
	activity is defined as ≥178.5 activity counts per minute; light physical activity is defined as 178.5 – 565.5 counts per minute; moderate-to-vigorous activity is defined as > 565.5 counts per minute. The average number of minutes per day spent in the different non-sedentary physical activity categories (light and moderate-to-vigorous) will be calculated over 14 day epochs. **Units of measure**: descriptive statistics for quantitative data. **Time frame**: baseline[1] epoch (i.e. week -2 to week 0), week 2 to week 4, week 6 to week 8, week 10 to week12.	
To assess the difference in non-sedentary daytime physical activity between sacubitril/valsartan vs. enalapril treated patients during the treatment period (weeks 0 to 12).	**Title**: Total weekly time spent in non-sedentary daytime physical activity. **Title**: Total weekly time spent in light non-sedentary daytime physical activity. **Title**: Total weekly time spent in moderate-to-vigorous non-sedentary daytime physical activity **Description:** Non-sedentary physical activity is defined as ≥178.5 activity counts per minute; light physical activity is defined as 178.5 – 565.5 counts per minute; moderate-to-vigorous activity is defined as > 565.5 counts per minute. The total time spent in non-sedentary physical activity and the time spent in light and moderate-to-vigorous physical activity will be calculated for each patient in weekly intervals and the temporal course for each patient will be assessed. **Units of measure**: descriptive statistics for quantitative data. **Time frame**: week 0 to week 12 in weekly epochs	Section 9.5
To assess changes from baseline[1] on M6min (an actigraphy-based measure of the peak six minutes of daytime physical activity) in sacubitril/valsartan vs. enalapril treated patients after week 4; week 8 and week 12.	**Title**: Change from baseline[1] in M6min. **Title**: Proportion of patients with increased M6min compared to baseline[1] at week 4, week 8 and week 12. **Description**: M6min is a parameter derived by validated algorithms of the software that will be used to pre-process actigraphy data. The	Section 9.5

[redacted]

Objective	Endpoint	Analysis
	parameter reflects the peak 6 minutes of physical activity. The mean daily M6min will be calculated over 14 day epochs. **Units of measure**: descriptive statistics for quantitative data, absolute and relative frequency distributions including 95% confidence intervals. **Time frame**: baseline[1] epoch (i.e. week -2 to week 0), week 2 to week 4, week 6 to week 8, week 10 to week12	

[redacted]

[redacted]

[1] For all objectives/endpoints assessed by means of actigraphy, the baseline value is obtained over a period of two weeks prior to randomization, i.e. weeks -2 to week 0.

3 Investigational plan

3.1 Study design

This is an international (European), randomized, actively controlled, double-blind, double-dummy, interventional study with prospective data collection. The study comprises 6 visits over 14 weeks. Adult patients with symptomatic HFrEF (NYHA classes II or III/IV at a 1:1 ratio, see Section 5.3) managed in an ambulatory setting (i.e. by primary care physicians, office based cardiologists, HF outpatient clinics) will be randomized in a 1:1 allocation to receive sacubitril/valsartan or enalapril during the double-blind period. Actigraphy will be performed during the entire duration of the study by means of a wrist-worn accelerometry device; the device will be worn continuously for two weeks prior to randomization in order to obtain an individual baseline for each patient, and throughout the treatment period of the study (12 weeks). Figure 3-1 depicts the study design along with the treatment and visit schedule.

Visit 1

Eligible patients, after signing informed consent, will receive the actigraphy device at Visit 1 (week -2). Eligible patients are those who satisfy all inclusion and exclusion criteria (Section 4), i.e. among other criteria, they have been on stable dose of at least enalapril 2.5 mg/d, or equivalent ACEI or ARB for at least 4 weeks prior to Visit 1 (see Table 3-1). The patients at this time should continue stable intake of their current ACEI/ARB, as well as concomitant medication, until the Visit 2 (week 0).

Table 3-1 Minimum required pre-study daily doses of commonly prescribed ACEIs and ARBs (considered equivalent to 2.5 mg/d enalapril)

ACEIs	Minimum daily dose	ARBs	Minimum daily dose
Enalapril	2.5 mg	Candesartan	4 mg
Benazepril	5 mg	Eprosartan	100 mg
Captopril	25 mg	Irbesartan	37.5 mg
Cilazapril	0.625 mg	Losartan	12.5 mg
Fosinopril	5 mg	Olmesartan	2.5 mg
Lisinopril	5 mg	Telmisartan	10 mg
Moexpril	3.75 mg	Valsartan	40 mg
Perindopril	2 mg		
Quinapril	5 mg		
Ramipril	1.25 mg		
Trandolapril	1 mg		
Zofenopril	7.5 mg		

Visit 2

At Visit 2 (week 0), patients will be randomized to receive either sacubitril/valsartan or enalapril; patients should continue to take their background medication for HF during the study, with the exception of ACEI or ARBs – these are replaced by the study treatment and must be discontinued 36 hours before first application of the study drug. The first application of the study drug is planned for the day after Visit 2 (randomization) – therefore the last intake of the patient's ACEI or ARB before commencing study drug intake should be on the evening before Visit 2 (e.g. if Visit 2 is scheduled for Wednesday the last ACEI or ARB medication should be taken by the patient on Tuesday evening. The patient will then start to take the first dose of study medication (sacubitril/valsartan or enalapril) on Thursday morning).

Treatment will be initiated depending on the patient's previous ACEI/ARB. Refer to Table 5-2). After 2 weeks (i.e. at Visit 3) the doses are up-titrated and after another 2 weeks (i.e. at Visit 4) all patients should have achieved the target dose of either 10 mg bid enalapril or 97 mg/103 mg bid sacubitril/valsartan, provided no safety and tolerability issues arise during up-titration. The titration steps for the three dose levels are described in detail in Section 5.5.4.

[redacted]

[redacted]

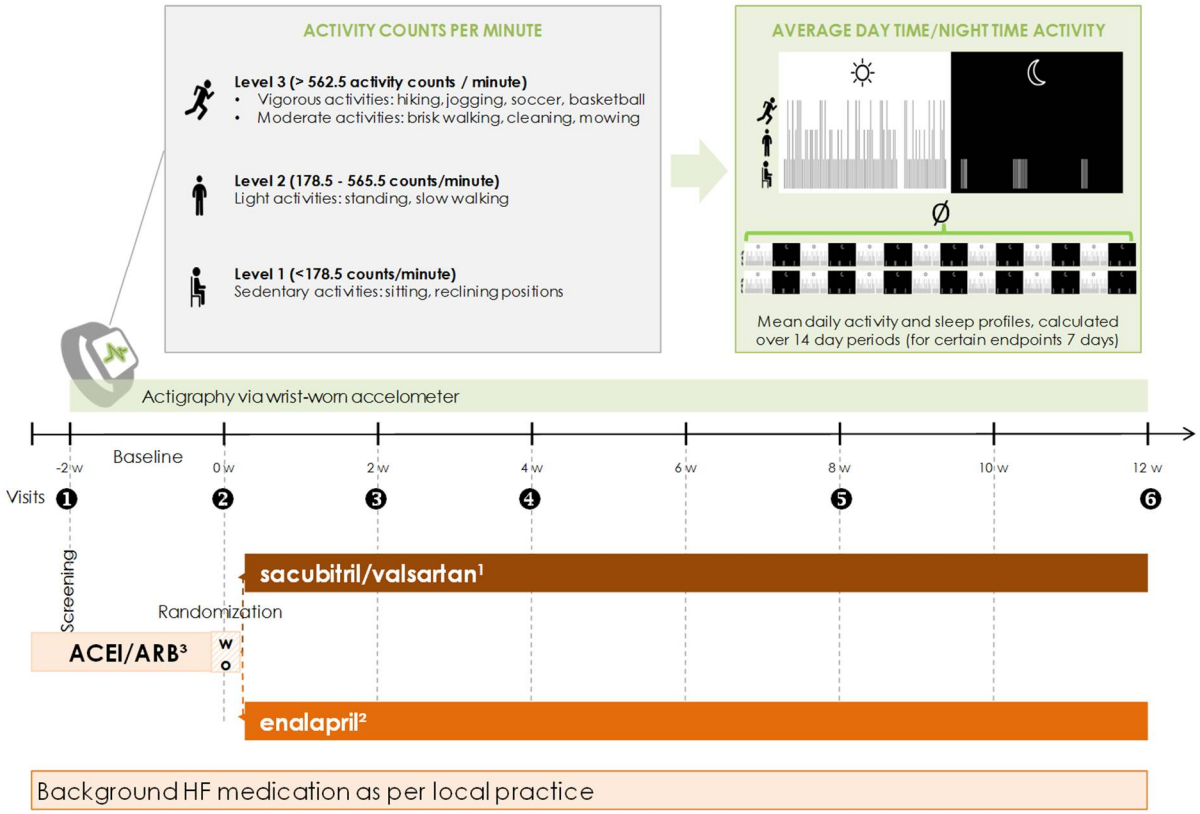
Note: according to the sacubitril/valsartan SmPC and the investigator's medical judgement, patients suffering from moderate hepatic impairment, moderate renal impairment or patients with SBP ≥100 to 110 mmHg should be initiated at dose level 1.

At this visit the baseline actigraphy data will be downloaded from the wrist-worn device.

Visit 3 to Visit 6

The visit schedule continues in two-weekly intervals until Visit 4 (week 4), where up-titration is expected to be finished for the majority of patients (see Section 5.5.4). Thereafter two more visits are planned in 4-weekly intervals (i.e. Visit 5 at week 8 and Visit 6 at week 12). At all visits, physical examination and current NYHA status is documented, as well as safety monitoring and adverse events. At Visit 4 and Visit 6, the data from the actigraphy device are downloaded; at Visit 4 the battery of the actigraphy device should be replaced according to the manual provided in the site folder. At Visit 4, Visit 5 and Visit 6 the [redacted] PGA, [redacted], [redacted] and the 6-minute walking test are performed and documented. Further information on the visit schedule and data collection scheme is found in Table 6-1.

Figure 3-1 Study design



[1-2] sacubitril/valsartan or enalapril (double-blind study drugs) will be given at dose levels (up-titration) depending on pre-study ACEI/ARB doses. See Table 5-1 regarding doses levels and Table 5-2 for titration scheme.

[3]Pre-study ACEI and/or ARB are replaced by study medication after Visit 2. Therefore washout period (WO) of 36 hours is required; it should start 12 hours before Visit 2 (randomization); the first study

[redacted]

treatment intake should be 24 hours after Visit 2.
All other HF background and CV medications (e.g. beta blockers, MRAs etc.) and symptomatic treatment (e.g. diuretics) the patient has been taking should remain unchanged throughout the study, if possible and medically justified in the judgement of the investigator.
"Background HF medication per local practice": patients must be on stable HF treatment regimen for at least 4 weeks prior Visit 1. After Visit 1, patients shall retain their pre-study HF treatment for another 2 weeks (week -2 to week 0) for baseline actigraphy recording.

3.2 Rationale for study design

The patient population will be described in more detail in the Section 4 below.

The aim of the present study is to assess differences between sacubitril/valsartan versus enalapril in improving exercise capacity and daily non-sedentary daytime physical activity of patients with HFrEF. For such comparative objectives, randomized, actively controlled, interventional trials with balanced (selected) study populations are the state of the art and allow for controlling the patients' treatment and thus reducing bias. The study is double-blind in order to avoid subjective bias in the 6MWT, PGA, [redacted] ratings; in addition, while actigraphy per se allows for obtaining objective measures of physical activity, blinding of the patients to their treatments is crucial in order to avoid a bias due to treatment expectations. Circadian activity profiles will be performed by means of wearable (wrist-worn) actigraphy devices in order to obtain objective activity readouts. As daytime activity as well as sleep profiles are highly individual, it is important to obtain a stable baseline as well as to monitor activity profiles continuously. These crucial features are incorporated into the present study design, as the patients receive and are asked to permanently wear (24 hours a day) the actigraphy device for the entire study duration of 14 weeks - including 2 weeks where they still receive their pre-study HF medication. The actigraphy device will record activity data every 30 seconds over the 14 weeks study duration, thus allowing for an great level of data completeness; these data will be integrated in two-weekly bins (weekly for certain endpoints, see Table 2-1), in order to obtain stable data for each patient and to minimize the effects of individual extremes (e.g. days with very high or very low activity). Finally, the study will be performed at centers in different European countries, thus allowing for analysis of country- and healthcare system effects. Taken together, the present randomized, actively-controlled, double-blind, double-dummy approach is the most suitable design for achieving the study objective of demonstrating a difference between sacubitril/valsartan versus enalapril in improving the daily physical activity in patients with HFrEF.

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

Strong clinical rationale for the target dose (97 mg/103 mg bid) as well as titration steps of sacubitril/valsartan is derived from the pivotal clinical trial PARADIGM-HF (McMurray et al., 2014) and this dosing schedule has been shown to be efficacious, safe (Senni et al., 2016) and is approved by the European Medicines Agency (EMA) for the treatment of symptomatic patients with chronic HF and reduced LVEF. The sacubitril/valsartan target dose of 97 mg/103 mg bid delivers an equivalent daily dose of valsartan as Diovan® 160 mg bid, the dose commonly recommended by current HF management guidelines (Ponikowski et al., 2016).

[redacted]

The twice-daily dosing regimen of sacubitril/valsartan also ensures a sustained neprilysin (NEP) inhibition over 24 hours.

3.4 Rationale for choice of comparator

Enalapril, the comparator chosen for this study, is an ACEI - the drug class considered a gold standard by current therapy guidelines for the treatment of HFrEF patients (Ponikowski et al., 2016). ACE inhibitors and enalapril in particular, are the pharmacological standard of care for HFrEF management in Europe and – according to the current label – sacubitril/valsartan can be used to replace ACEI or ARBs in the management of HF. Furthermore, in the pivotal clinical trial PARADIGM-HF (McMurray et al., 2014), enalapril was the active comparator for sacubitril/valsartan. Thus, enalapril was chosen as the active comparator for the present study. Enalapril will be used in this study according to its label and recommended dosing of 10 mg bid, which is the most commonly recommended target dose for HFrEF patients and has been shown to reduce the risk of death and hospitalizations in HF patients (SOLVD, 1992).

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

Both treatments, sacubitril/valsartan and enalapril, are approved for the treatment of the studied indication. Please refer to the Summary of Product Characteristics (SmPC) of the corresponding products as well as the Investigator's Brochure (IB) of sacubitril/valsartan for information on known adverse drug reactions or special precautions with both investigational medicinal products (IMPs).

Patients will be instructed not to take any renin angiotensin aldosterone system (RAAS) blocking agents (ACEIs or ARBs) within 36 hours prior to start of study treatment in order to avoid excessive RAAS inhibition. The risks associated with the temporary discontinuation of RAAS blockade (36h washout period) is minimal as it represents a common safety measure also performed in clinical routine outside of clinical trials; in addition, RAAS blockade represents only one pillar of pharmacotherapy for HFrEF and the patients other HF medication (so called background HF medication), such as beta-blocking agents or mineralocorticoid receptor antagonists (MRAs) will not be altered due to study participation. The risk of excess RAAS inactivation will be mitigated by the 36h washout period, as well as the staggered titration of study medication (see Table 5-2).

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

In women of child-bearing potential, a possible risk of developmental toxicity cannot be excluded. Thus, women of child-bearing potential should use a highly effective method of contraception during dosing and for 7 days off study medication as described under Section 4.2.

Participating patients will benefit from careful monitoring and follow-up during the entire study.

[redacted]

The current study aims to elucidate the short term effects of sacubitril/valsartan compared to enalapril on physical activity of HFrEF patients considering the period between treatment initiation, achievement and first maintenance of a stable tolerated dose, as such data currently are not available. However, due to the proven long-term superiority of sacubitril/valsartan over enalapril in terms of reduced mortality and morbidity shown in PARADIGM-HF (McMurray et al., 2014), the duration of the double-blind, randomized treatment phase of the present study was limited to a total of 12 weeks, which allow for an up-titration and maintenance of a stable tolerated dose, but is short enough to mitigate the risk for the patients due to treatment blinding. Furthermore, the treatment regimens stipulated within the present protocol are compliant with the recommendations on pharmacological treatment of HFrEF patients, as defined in the current ESC Guidelines for the treatment in ambulatory HFrEF patients (Ponikowski et al., 2016).

4 Population

The study population will consist of adult (≥ 18 years old) male and female patients with symptomatic HFrEF who are ambulatory managed by a primary care physician, office-based cardiologist or in HF outpatient clinics for their HF. The goal is to randomize a total of 600 patients at ~132 sites across Europe. Eligible patients should be on a stable HF treatment for at least 4 weeks prior to screening; the required minimal doses of pre-study ACEI or ARB are listed in Table 3-1.

The investigator must ensure that all patients who satisfy all inclusion and exclusion criteria are offered enrollment in the study. No additional parameter can be applied by the investigator.

4.1 Inclusion criteria

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

1. Written informed consent obtained before any study assessment is performed.
2. Ambulatory ≥ 18 years of age with a diagnosis of chronic symptomatic HF (NYHA class ≥ II) with reduced ejection fraction, defined as known LVEF ≤ 40% (known LVEF ≤ 40% at Visit 1 reflects any local measurement, made within the past 12 months using echocardiography, MUGA, CT scanning, MRI or ventricular angiography, provided no subsequent measurement with LVEF results above 40% is available).

   AND one of the following two criteria:

   - Plasma NT-proBNP level of ≥ 300 pg/mL or BNP ≥ 100 pg/mL (measurement may be recorded no longer than past 12 months)

   OR

   - Confirmation of a heart failure hospitalization last 12 months
3. Patients must be on stable HF medication (i.e. ACEI/ARB, beta-blockers and MRA) for at least 4 weeks prior to Visit 1, where the minimal daily dose of ACEI/ARB dose is equivalent to at least 2.5 mg/d enalapril (see Table 3-1).
4. Willingness to wear the accelerometer wristband continuously for the duration of the trial.

[redacted]

5. Patients must be living in a setting, allowing them to move about freely and where they are primarily self-responsible for scheduling their sleep and daily activities.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria 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 patients/subjects.

1. Use of other investigational drugs within 5 half-lives, or within 30 days of enrollment, whichever is longer.
2. History of hypersensitivity to any of the study drugs or their excipients or to drugs of similar chemical classes
3. Use of sacubitril/valsartan prior to Visit 1.
4. Known history of angioedema (any kind of angioedema i.e. hereditary, idiopathic, angioedema related to previous drug use such as ACEI).
5. Bedridden patients, or patients with significantly impaired/limited physical activity and/or fatigue due to medical conditions other than HF, such as, but not limited to angina (chest pain at exertion), arthritis, gout, peripheral artery occlusive disease, obstructive or restrictive lung disease, malignant disease, neurological disorders (e.g. Parkinson's or Alzheimer's disease, central and peripheral neuroinflammatory and -degenerative disorders or functional central nervous lesions due to hemodynamic or traumatic incidents), injuries (incl. diabetic foot ulcers) or missing limbs.
6. Patients with significant chronic obstructive pulmonary disease (COPD) contributing to dyspnea or patients whose COPD medication has been altered within 4 weeks prior to Visit 1.
7. Patients with palsy, tremor or rigor affecting the non-dominant arm.
8. Patients with any skin or other condition of the non-dominant arm that would limit the ability to wear the actigraphy device continuously (24h/day) over 14 weeks.
9. Patients fully depending on a mobility support system, e.g. wheelchair, scooter or walker. Patients are allowed to use a cane as long as this is not used with the non-dominant arm.
10. Patients requiring a dual RAAS blockade (i.e. treatment with both ACEIs and ARBs or concomitant treatment with aliskiren)
11. Patients with acute decompensated HF within 4 weeks of Visit 1, i.e. exacerbation of chronic HF manifested by signs and symptoms that may require intravenous therapy.
12. Symptomatic hypotension and/or a systolic blood pressure (SBP) < 100 mmHg at Visit 1 (screening) or at Visit 2 (randomization).
13. Estimated GFR (eGFR) < 30 mL/min/1.73 m² as calculated by simplified MDRD formula at Visit 1 or Visit 2
14. Serum potassium > 5.4 mmol/L at Visit 1 or at Visit 2
15. Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid or other major vascular surgery, percutaneous coronary intervention (PCI) or carotid angioplasty within 3 months prior Visit 1.
16. Coronary or carotid artery disease likely to require surgical or percutaneous intervention within the 14 week study duration.

[redacted]

17. Implantation of cardiac resynchronization therapy pacemaker (CRT-P) or -defibrillator (CRT-D) or upgrading of an existing conventional pacemaker or implantable cardioverter defibrillator (ICD) to a CRT device within 3 months prior to Visit 1 or intended/planned such procedure within the 14 weeks study duration; patients with a implantation of conventional pacemaker or an ICD or with a revision of a pacemaker or other device electrodes within 1 month prior to Visit 1 are also excluded.
18. Patients with existing or planned/intended heart transplant or ventricular assistance device (VAD).
19. Diagnosis of peripartum or chemotherapy induced cardiomyopathy within 12 months prior to Visit 1.
20. Documented untreated ventricular arrhythmia with syncopal episodes within 3 months prior to Visit 1.
21. Symptomatic bradycardia or second or third degree of cardiac electrical conduction without a pacemaker.
22. Hemodynamically significant mitral and/or aortic valve disease, except mitral regurgitation due to ventricular dilatation.
23. Other hemodynamically significant obstructive lesions of left ventricular outflow, including aortic and sub-aortic stenosis.
24. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of study drugs, including but not limited to:
    - History of active inflammatory bowel disease during 12 months before Visit 1.
    - Current duodenal or gastric ulcers during the 3 months prior to Visit 1.
25. Evidence of hepatic disease as determined by any one of the following: AST or ALT values exceeding 2 x upper limit of normal (ULN) at visit 1, severe hepatic insufficiency (classification Child-Pugh C), biliary cirrhosis, cholestasis (current or anamnestic evidence), history of hepatic encephalopathy, history of esophageal varices, history of portocaval shunt.
26. Current or planned active treatment with bile sequestering agents such as cholestyramine, colestipol resins, colesevelam, or similar medication.
27. Patients with bilateral renal artery stenosis.
28. Patients with thyroidal dysfunction who have not been on a stable dose L-thyroxin within the last 3 months prior Visit 1.
29. Patients with Graves' disease.
30. Patients with severe adipositas (adipositas per magna – BMI $\geq$ 40).
31. Patients with ongoing alcohol or drug abuse or dependence.
32. Documented long QT syndrome or QTc > 450 msec for males and 470 msec for females within 3 months prior to Visit 1.
33. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
34. 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 (> 5 mIU/mL)

[redacted]

35. 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 further 7 days. Highly effective contraception methods include:
    - 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
    - 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
    - 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
    - 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.
    - Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

All eligible patients will be randomized in a 1:1 allocation to receive either sacubitril/valsartan or enalapril in addition to their individualized cardiovascular (CV) medication (i.e. background HF medication) as considered appropriate by the investigator but with exception of ACEI or ARBs which will be replaced by the investigational treatment. Thus the use of an ACEI or an ARB is allowed only during the baseline recording period (week -2 to week 0, where patients remain on their already existing HF treatment regimen), but is strictly prohibited beyond the day prior to randomization when a 36 hour washout period for ACEIs and ARBs commences. During the dosing of study medication, i.e. beyond randomization until the end of the study, the intake of ACEIs or ARBs remains prohibited.

The following study drugs will be provided:

- sacubitril/valsartan 24 mg/26 mg film-coated tablets (LCZ696 50 mg dose level 1)

[redacted]

- placebo to match sacubitril/valsartan 24 mg/26 mg film-coated tablets (placebo matching LCZ696 50 mg dose level 1)
- sacubitril/valsartan 49 mg/51 mg film-coated tablets (LCZ696 100 mg dose level 2, dose level 2a)
- placebo to match sacubitril/valsartan 49 mg/51 mg film-coated tablets (placebo matching LCZ696 100 mg dose level 2, dose level 2a)
- sacubitril/valsartan 97 mg/103 mg film-coated tablets (LCZ696 200 mg dose level 3)
- placebo to match sacubitril/valsartan 97 mg/103 mg film-coated tablets (placebo matching LCZ696 200 mg dose level 3)
- enalapril 2.5 mg film-coated tablets (enalapril dose level 1)
- placebo to match enalapril 2.5 mg film-coated tablets (placebo matching enalapril dose level 1)
- enalapril 5 mg film-coated tablets (enalapril dose level 2)
- placebo to match enalapril 5 mg film-coated tablets (placebo matching enalapril dose level 2)
- enalapril 10 mg film-coated tablets (enalapril dose level 3, dose level 2a)
- placebo to match enalapril 10 mg film-coated tablets (placebo matching enalapril dose level 3, dose level 2a)

Target doses: sacubitril/valsartan 97 mg/103 mg bid (total daily dose 194 mg/206 mg) and enalapril 10 mg bid (total daily dose 20 mg).

All tablets provided have different shapes and colors. Thus, the study will employ a double-blind, double-dummy design to ensure blinding during its entire course. To this end, patients will receive their assigned active study treatment as well as placebo matching the opposite treatment. The patients are required to take study medication twice daily (bid: meaning in the morning and in the evening) along with their concomitant medication (as prescribed by their treating physician).

All doses of sacubitril/valsartan and its matching placebo will be provided in HDPE bottles. Enalapril 2.5 mg and its matching placebo will be provided in HDPE bottles, while the other doses of enalapril and its matching placebo will be provided in blister packs.

5.1.2 Additional treatment

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

5.2 Treatment arms

Patients who are eligible for randomization at Visit 2 will be assigned to one of the following two treatment arms in a 1:1 ratio:

- sacubitril/valsartan and placebo matching enalapril bid
- enalapril and placebo matching sacubitril/valsartan bid

[redacted]

5.3 Treatment assignment and randomization

At Visit 2 all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients/subjects and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management (DSM) using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

A proportionate stratified random sampling will be performed using the NYHA class at Visit 1 as stratification parameter (i.e. patients with NYHA class II or III/IV). This approach will ensure balanced allocation of patients to treatment groups within the NYHA class strata. Additionally, the proportionate sampling aims to allow the study population to achieve a similar proportion of patients with NYHA II and patients with NYHA III or IV as expected in the general population of adult HFrEF patients. Based on the literature (Jonsson et al., 2010, Salvador et al., 2004, Sartipy et al., 2014, Tebbe et al., 2014) this ratio is assumed to be close to 1:1 and proportionate sampling will be performed accordingly.

5.4 Treatment blinding

Patients/subjects, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods:

1. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions:
   - Specific vendors whose role in the trial conduct requires unblinding (e.g. IRT)
   - Drug supply management (DSM).
2. The identity of the treatments will be concealed by the use of study drug that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.
3. A double-dummy design is used because the identity of the study drug cannot be disguised, as the drug products are visibly different.

Unblinding will only occur in the case of patient emergencies (see Section 5.6) and at the conclusion of the study.

[redacted]

5.5 Treating the patient

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

5.5.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the investigative site.

Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 1, and subsequent patients/subjects are assigned consecutive numbers (e.g. the second patient is assigned patient number 2, the third patient is assigned patient number 3). The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomized for any reason, the IRT must be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Log, and the Demography eCRF should also be completed.

5.5.2 Dispensing the study drug

Each study site will be supplied by Novartis with study drug in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the two treatment arms and a specific dose level. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, 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 patient's unique subject number.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and 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. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient 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. Patients will be asked to return all unused study

[redacted]

treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Novartis will supply the investigators with all study medication sufficient for the course of the study. Patients will be provided with medication packs containing the study drug corresponding to their assigned treatment arm and dose level, sufficient to last until their next scheduled visit. Site personnel must ensure to plan the study visits within 35 days to ensure that the patient by all times have sufficient study drug. In order to maintain blinding, patients will be required to take two tablets (one sacubitril/valsartan or its matching placebo and one enalapril or its matching placebo) twice a day for the duration of the study. The dose levels of study medication that will be used for titration purposes are shown in Table 5-1.

Table 5-1 Study drug dose levels

Dose level	Sacubitril/valsartan	Enalapril
3*	97 mg/103 mg or matching placebo bid	10 mg or matching placebo bid
2a#	49 mg/51 mg or patching placebo bid	10 mg or matching placebo bid
2	49 mg/51 mg or matching placebo bid	5 mg or matching placebo bid
1	24 mg/26 mg or matching placebo bid	2.5 mg or matching placebo bid

*This dose level must be maintained for as long a duration as possible. If a down-titration is necessary due to side effects, the patient should be re-challenged as soon as possible, per the investigator's judgement. In case down-titration is necessary due to tolerability issues, down-titration is possible to dose level 2 or 0.

Level 2a is only a starting dose level for patients who received a pre-study Enalapril total daily dose above 10 mg/d (or equivalent dose of other ACEI/ARB).

Patients will begin study treatment at a dose level according to their pre-study ACEI or ARB dose (enalapril equivalent dose, also see Table 3-1. Patients who had a pre-study enalapril total daily dose of <5 mg/d (or equivalent dose of other ACEI/ARB) will start study medication at dose level 1 (see Table 5-1). Patients with a pre-study enalapril total daily dose of ≥5 mg/d to 10 mg/d (or equivalent dose of other ACEI/ARB) will start study medication at dose level 2. Patients with a pre-study enalapril total daily dose of >10 mg bid (or equivalent dose of other ACEI/ARB) will start study medication at dose level 2a.

Note: according to the sacubitril/valsartan SmPC and the investigator's medical judgement, patients suffering from moderate hepatic impairment, moderate renal impairment or patients with SBP ≥100 to 110 mmHg should be initiated at dose level 1.

[redacted]

Two weeks (Visit 3) after randomization, up-titration is performed to the next higher level, provided good tolerability of the starting dose level; this means that patients, who started on dose level 2 or 2a will receive the target dose of study medication (level 3) at this point. Patients, who started study medication at dose level 1, will have a final up-titration after additional 2 weeks, i.e. at Visit 4. Therefore, after Visit 4 all patients will be receiving the target dose (level 3), unless safety issues prevent up-titration, or down-titration becomes necessary (see Section 5.5.4). See the following Table 5-2 for an overview of up-titration scheme of study medication according to pre-study ACEI/ARB total daily dose.

Table 5-2 Study drug titration according to previous ACEI/ARB dose

Enalapril total daily dose before Visit 1 (week -2) (or equivalent dose of other ACEI/ARB, see Table 3-1)	Study drug dose level after randomization at Visit 2 (week 0)	Up-titration at Visit 3 (week 2)	Up-titration at Visit 4 (week 4)
< 5.0 mg/day	Dose level 1	Dose level 2	Dose level 3
5.0 mg to ≤ 10 mg/day	Dose level 2	Dose level 3	
>10 mg/day	Dose level 2a	Dose level 3	

Note: according to the sacubitril/valsartan SmPC and the investigator's medical judgement, patients suffering from moderate hepatic impairment, moderate renal impairment or patients with SBP ≥100 to 110 mmHg should be initiated at dose level 1.

All kits of study treatment assigned by the IRT will be recorded/databased in the IRT.

Patients will be instructed to take the study medication twice daily – once in the morning and once in the evening. The morning study drug dose should occur around 08.00 (8 am), the evening dose at approximately 19.00 (7 pm). The study medication should be taken with a glass of water with or without food. If the patient misses taking any study dose, he/she should take it as soon as possible, unless it is almost time for the following scheduled dose. In this case, the patient should be instructed to skip the missed dose and return to his/her regular study drug intake schedule.

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

5.5.5 Permitted dose adjustments and interruptions of study treatment

Once patients achieve the target study drug dose, every attempt should be made to maintain the target study drug dose level for as long as possible throughout the trial.

If, however, in the opinion of the investigator, the patient does not tolerate the target dose of the study drug, the investigator should consider whether non-disease modifying medication (e.g. calcium channel blockers, diuretics, nitrates or alpha-blockers) can be reduced to rectify the situation, before considering to reduce the dose of study drug to the next lower dose level. In addition, the investigator may adjust the doses of disease-modifying medications, if he/she believes that they are more likely causes of adverse events. If such adjustments of

[redacted]

concomitant medications are not medically indicated, the investigator may down-titrate the dose of study drug to the next lower dose level up to a complete withdrawal of the investigational treatment, if necessary. In such cases, the patient should be re-challenged with the higher dose level when the investigator feels that doing so is appropriate; the re-challenge should be performed according to the guidance provided in this section (see below) of the protocol.

If necessary, study drug may be stopped completely, but the patients should continue to attend study visits and be followed until completion of the study.

Study drug dose level adjustments should be based on overall safety and tolerability with a special focus on

- Hyperkaliemia (see Appendix 1 and Appendix 4 for guidelines for managing hyperkaliemia)
- Symptomatic hypotension (see Appendix 5 for guidelines on BP management)
- Clinically significant decrease in eGFR or clinically significant increase in serum creatinine (see Appendix 1 and Appendix 6 for guidelines on managing renal dysfunction)
- Worsening hepatic function (see Appendix 2)

For patients/subjects who are unable to tolerate the protocol-specified dosing scheme, dose adjustments and interruptions of investigational drug are permitted in order to keep the patient on study drug.

The following guidelines must be followed:

Adjustment of study drug dose level

During the double-blind treatment period down-titration of the study drug is allowed at any time based on the safety and tolerability criteria defined in Appendix 1, Appendix 14, Appendix 3 and Appendix 4. If down-titration is necessary, the next lower dose level should be prescribed (see Table 5-1; Please note, that dose level 2a is only allowed as a starting dose). The patient may continue receiving the lower dose level for a recommended period of one to two weeks before re-challenging the patient with the next higher dose level. For example: a patient who encounters tolerability issues at the target dose level (level 3) should receive the study drug at dose level 2 for one to two weeks, before he/she is re-challenged with an up-titration back to dose level 3.

If the first initial dose reduction does not lead to alleviation of the tolerability issues, the investigator may lower the study drug dose further to the next lower level for another one to two weeks. If necessary, the study drug may be temporarily withdrawn. Once stable, the patient should be re-challenged with the next higher dose level every one to two weeks in an attempt to gradually up-titrate he patient to receive the target dose (level 3) (Table 5-1).

In some cases, according to the safety and tolerability criteria described above and the investigator's judgement, the study drug dose level 2 could be maintained if the patient's condition does not allow up-titration (or re-challenge) to the target dose (dose level 3). In these cases, it is acceptable to maintain the patient on dose level 2. Similarly, if dose level 2 is not tolerated by the patient, a down-titration to dose level 1 is allowed and, if necessary and

justified within the judgement of the investigator, the patient may be maintained on dose level 1, if up-titration or re-challenge is not tolerated by the patient.

Study drug re-start after temporary treatment interruption

Study drug should be re-introduced in patients for whom a temporary interruption becomes necessary; if possible and medically justified in the judgement of the investigator the duration of the interruption should be one to two weeks.

Once the investigator considers the patient's condition appropriate for re-introducing the study drug, the investigator should re-start the study drug at the most appropriate dose level (Table 5-1, Note, that dose level 2a, is only for initial dose and will not be available for up-titration after re-start) according to his/her judgement. If the safety and tolerability criteria (see above and Appendix1, Appendix 2, Appendix 3 and Appendix 4) are not violated, the patient's study drug dose should be up-titrated after re-starting every one to two weeks to the next higher level, until the target dose level is reached. If the patient does not tolerate the up-titration after temporary treatment interruption, the dose can be down-titrated again (if appropriate) or study drug should be discontinued.

Patients who are re-started after temporary interruption of the study drug will retain their initial randomization and study identification numbers.

Note for all dose adjustments: These changes will be tracked in the IRT system.

5.5.6 Rescue medication

Guidance on handling hyperkaliemia, hypotension and renal dysfunction are provided in Appendix1, Appendix 4, Appendix 5 and Appendix 6. If necessary, patients may receive open-label ACEI and/or ARBs ONLY if study medication is interrupted temporarily or discontinued permanently. NOTE that a washout phase of 36 hours is required for the study drug, but also for any ACEI or ARB before (re-)introducing study drug.

Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies Record in the CRF.

5.5.7 Concomitant medication

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

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 randomizing a patient or allowing a new medication to be started.

The patients' pre-study ACEIs or ARBs will be replaced by the study drug. As per inclusion criteria, the patients need to be on stable HF therapy regimen for at least 4 weeks prior to Visit 1 and should remain on a stable regimen, if medically justified, throughout the entire study duration.

[redacted]

Diuretics may be used and may be adjusted at any time throughout the duration of the study at the discretion of the investigator.

Potassium-sparing diuretics (e.g. amiloride), potassium supplements, mineralocorticoid receptor antagonists (e.g. spironolactone) and any other medications known to raise potassium levels should be used with caution while the patients receive study medication, due to increased possibility of hyperkaliemia. The investigators are encouraged to assess patients' potassium levels regularly, especially during the up-titration and in those receiving such medications.

Phoshodiesterase-5 inhibitors should be used with caution while patients receive study medication due to increased possibility of occurrence of hypotension.

Caution should be exercised upon co-administration of statins such as atorvastatin, pravastatin or pitavastatin and study medication, due to potential interactions between statins and sacubitril/valsartan. Similarly, potential interactions between sacubitril/valsartan and lithium or non-steroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase-2 (COX-2) inhibitors should be considered.

Due to potential drug interactions between ACE-inhibitors and specific anti-diabetic medication (such as insulins, specific oral hypoglycemic agents) as well as potential interaction between metformin and sacubitril/valsartan, patients on antidiabetic treatment are encouraged to be followed up to ensure adequate management of their diabetes according to investigators discretion.

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-3 is NOT allowed after the start of the washout period, i.e. the evening before Visit 2. Note, during the baseline recording period, i.e. over two weeks after Visit 1 (i.e. week -2 until 12 hours before Visit 2) the patients will receive their usual pre-study medication to obtain a baseline.

ACEIs and/or ARBs are replaced by study medication and therefore need to be discontinued 12 hours before Visit 2 (i.e. the evening before Visit 2). At Visit 2, patients will be randomized to receive either sacubitril/valsartan or enalapril; the patients will receive the first dose of study medication 24h after the randomization visit, resulting in a washout period from ACEIs or ARBs of 36 hours. In order to avoid excessive RAAS inhibition, it is crucial to respect the washout period and instruct the patient to not take any ACEI or ARB while taking double-blind study medication.

Direct renin inhibitors (i.e. aliskiren) are also prohibited for safety reasons, as concomitant intake of renin inhibitors and study medication could increase the likelihood of occurrence of hyperkaliemia.

Bile acid sequestering agents are prohibited due to potential interference with the absorption of study drugs.

[redacted]

Table 5-3 Prohibited medication

Medication	Action taken
Any ACEI, Any ARB, Renin inhibitors	Discontinue these drugs starting at 12h before Visit 2, prohibited until at least 36 hours after study drug discontinuation/interruption/end of study. In case these drugs are taken / need to be taken during the double-blind treatment period of the study, discontinue study drug.
Bile acid sequestering agents (e.g. cholestyramine, colestipol)	Discontinue before randomization, prohibited throughout the study. No action required with study medication.

5.5.9 Emergency breaking of assigned treatment code

Emergency treatment code breaks must only be undertaken when it is required in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- patient number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

After an emergency treatment code break, the patient must discontinue study treatment.

In case of accidental unblinding, Novartis personnel and the investigator will decide on the patient's continuation of the trial.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. This care may

[redacted]

include initiating another treatment outside of the study as deemed appropriate by the investigator

5.6.2 Discontinuation of study treatment

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

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Pregnancy (see Section 6.5.5 and Section 7.9)
- Use of prohibited treatment as per recommendations in Table 5-3
- Any situation in which study participation might result in a safety risk to the patient.
- Suspected occurrence of angioedema. A patient with any signs of symptoms of clinically significant angioedema should be thoroughly evaluated by the investigator. Clinically significant angioedema constitutes a reason for temporary interruption or permanent discontinuation of study drug.

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

- Any severe suspected drug-related adverse event (AE)
- If safety and tolerability criteria are met, as defined in Appendix 1, Appendix 2, Appendix 3 and Appendix 4.
- Any other protocol deviation that results in a significant risk to a patient's safety.

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study. The patient should return to the clinic as soon as possible, after discontinuation of the study drug, for a study treatment discontinuation visit. Treatment discontinuation visit assessments detailed in the "unscheduled visit" (UNS) in Table 6-1 should be completed and recorded in the eCRF. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information in the source data and the Study Discontinuation page.

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

- new / concomitant treatments
- adverse events/Serious Adverse Events

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

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

[redacted]

Please note that the End of Study Visit (EOS) should be performed for all patients who either complete the study or discontinue the treatment, but start the abbreviated visits and for patients who prematurely discontinued the study.

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9

5.6.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient:

- 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

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

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

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

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

5.6.4 Loss 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 should 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 patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 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, alternations in accepted clinical practice that make the continuation of the trial unfeasible, or for regulatory or reasons or insufficient patient recruitment. Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator

[redacted]

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

Table 6-1 lists all of the assessments and indicates with an "x" when the assessments are performed.

Patients/subjects must be seen for all visits on the designated day, or as close to it as possible with an allowed "visit window" defined in Table 6-1. Missed or rescheduled visits should not lead to automatic discontinuation. Patients/subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments will be performed (EOS visit). At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF. Please note that patients who discontinue the study treatment and come to the unscheduled visit (UNS), study drug, tablet and motionwatch should be returned.

Patients will be contacted for safety evaluations until the 30 days following the last administration of study treatment. Evaluations can be made by phone and should be documented in the source data.

[redacted]

Table 6-1 Assessment schedule

Epoch	**Screening**	**Double-blind Treatment**							**Notes**
Visit	**1**	**2**	**3**	**4**	**5**	**6 (EoS)**	FU Call	*uns*	
Day *(Week)*	**-14 (-2)**	**1 (0)**	**14 (2)**	**28 (4)**	**56 (8)**	**84 (12)**	Up to 30 days after last drug dose		
Visit Window	**-3/+1**		**-3/+3**	**-3/+3**	**-5/+5**	**-1/+5**			the interval between the visits must not exceed 35 days as study comes in pre-filled packages for 35 days of treatment
Obtain informed consent	X								
Inclusion/Exclusion criteria	X	X							Some exclusion criteria apply for both Visit 1 and Visit 2
Demography	X								
Medical History / Current medical conditions	X								
Previous and concomitant drug/non-drug treatments	X	X	X	X	X	X		X[1]	Previous treatments will only be recorded for prior discontinued HF drug and non-drug therapy
Physical Exam	S	S	S	S	S	S		S[1]	At Visit 1, a full physical exam is performed; at all other visits a short exam is to be performed (see Section 6.5.1)
Height	X								
Weight	X					X			
Vital signs	X	X	X	X	X	X		X[1]	
Determine NYHA class	X	X	X	X	X	X		X[1]	
6-minute walking test		X		X	X	X			
[redacted]									
PGA				X	X	X			Patient's Global Assessment
[redacted]									
Contact IVRS/IWRS		X	X	X	X	X		X	At randomization, at study drug dispensation and at any time in case of study treatment discontinuation or emergency unblinding

[redacted]

Epoch	**Screening**	**Double-blind Treatment**							**Notes**
Visit	**1**	**2**	**3**	**4**	**5**	**6 (EoS)**	FU Call	*uns*	
Day *(Week)*	**-14 (-2)**	**1 (0)**	**14 (2)**	**28 (4)**	**56 (8)**	**84 (12)**	Up to 30 days after last drug dose		
Visit Window	**-3/+1**		**-3/+3**	**-3/+3**	**-5/+5**	**-1/+5**			the interval between the visits must not exceed 35 days as study comes in pre-filled packages for 35 days of treatment
Dispense Study Medication		X[3]	X	X	X			X	See Table 5-1 and Table 5-2 for dosing levels and titration. For patients who discontinue the treatment study drug should be returned.
Training patient on use of actigraphy device	X								
Download actigraphy data from patient's device		X		X		X		X[1]	
Change Actigraphy Device				X					
Adverse event monitoring	X	X	X	X	X	X	X	X[1]	
Urine pregnancy test		S				S		S[1]	Additional testing should be done as per local laws and regulations
Diagnostic and Laboratory evaluations									
Potassium	X	X	X	X	X	X		X[1]	also as per discretion of investigator (local lab)
AST and ALT	X	X	X	X	X	X		X[1]	also as per discretion of investigator (local lab)
Creatinine / eGFR	X	X	X	X	X	X		X	also as per discretion of investigator (local lab)
ECG	X[4]								
NT-proBNP	X#	X#	X#	X#	X#	X#		X#	Only if available – not required by the protocol during visit
Hemoglobin	X#	X#	X#	X#	X#	X#		X#	Only if available – not required by the protocol during visit
LVEF	X#	X#	X#	X#	X#	X#		X#	Only if available – not required by the protocol during visit

X = assessment to be recorded on clinical data base; S = assessment to be recorded on source documents only

[1]These assessments are to be conducted for patients who early discontinue the treatment and for all other reasons an unscheduled visit is needed (see details below). If a patient prematurely discontinues the study, an EOS should be performed. The UNS visit should also be done for patients who discontinue the treatment and continue the abbreviated visits until EOS.

[redacted]

[redacted]

Epoch	**Screening**	**Double-blind Treatment**							**Notes**
Visit	**1**	**2**	**3**	**4**	**5**	**6 (EoS)**	FU Call	*uns*	
Day *(Week)*	**-14 (-2)**	**1 (0)**	**14 (2)**	**28 (4)**	**56 (8)**	**84 (12)**	Up to 30 days after last drug dose		
Visit Window	**-3/+1**		**-3/+3**	**-3/+3**	**-5/+5**	**-1/+5**			the interval between the visits must not exceed 35 days as study comes in pre-filled packages for 35 days of treatment

[3] Study Medication will be dispensed but not be taken until the next day

[4] Only if no ECG has been performed within the last 3 months

assessments not required by the protocol, however if available within the diagnostic routine, they should be entered in the study data base

uns – unscheduled visit; when deemed necessary, unscheduled visits may be performed to ensure adequate medical management. This is exemplified by, but not limited to, patients achieving target dose at visit 4 and are perceived as fragile and thus need an extra monitoring visit, NYHA IV, renal impairment, patients prone to hypotension and or hepatic impairment. Investigator's clinical judgement and discretion is advised.

[redacted]

6.1 Information to be collected on screening failures

All patients/subjects who have signed informed consent but not entered into the next epoch (i.e. who were not randomized) 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. Collected actigraphy data will be downloaded by the investigator and recorded in the study data base.

Re-screening

If a patient is not eligible to enter the double-blind treatment epoch (i.e. screening failures), the investigator may consider re-screening the patient at a later time, if he/she believes that the patient's condition has changed and the patient may be potentially eligible. However, re-screening will only be possible for inclusion criterion 3 and exclusion criteria 1, 6, 11, 15, 17, 20, as well as 28. In this case, a completely new patient number will be allocated to the patient and all Visit 1 assessments will be performed again.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: year of birth, age, sex, race, ethnicity, source of patient referral (if applicable), the patients' living conditions, smoking status, relevant medical history/current medical condition present before signing informed consent (where possible, diagnoses and not symptoms will be recorded) previous drug/non-drug therapy of HF (prior Visit 1), concomitant medication and non-drug therapy.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.3 Treatment exposure and compliance

Adherence will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient. This information should be captured in the source document at each visit. The patients' compliance should at least be 80 % (i.e. the patient took at least 80 % of the tablets that were to be taken in the respective time period) during the double-blind treatment epoch. If compliance is below this threshold the investigator or study personnel will counsel the patient. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.4 Efficacy

Efficacy will be assessed by means of

- Actigraphy-derived parameters
- 6-minute walking test (6MWT)
- Patient Global Assessment questionnaire (PGA)

[redacted]

[redacted]

6.4.1 Actigraphy

Actigraphy is a non-invasive method of monitoring human physical activity patterns. Actigraphy will be performed in this study by means of a wrist-worn device that collects data on activity (by means of tri-axial accelerometry). The device (MotionWatch8®, CamNtech, Cambridge, UK) collects the data on movement continuously in 30-second bins. The device is lightweight and waterproof and worn on the wrist of the non-dominant arm continuously (24 hours/day) for the entire study duration. Based on accelerometry for each 30-second bin, activity counts for each minute of each day are generated. Higher counts reflect a higher level of activity. For an elderly population, cut-off values for activity counts per minute defining the intensity of physical activity have previously been defined (Landry et al., 2015) . These cut-off values will be used to define sedentary, light and moderate to vigorous activity counts for each minute the device is worn. Sedentary activity is defined as < 178.5 activity counts per minute; light activity as 178.5 – 565.5 activity counts/minute and > 565.5 activity counts/minute define moderate to vigorous physical activity (see also Figure 3-1). The time patients spend in a given activity intensity category will be recorded and represents the basis for all endpoints that are derived from actigraphy. Where appropriate, activity data will be integrated over 2-week intervals (i.e. baseline non-sedentary physical daytime activity is the mean time per day the patient spent in non-sedentary activity during the daytime during the 14 days of baseline recording (week -2 to week 0).

[redacted]

6.4.2 Six minute walking test

The distance covered by the patient walking during 6 minutes will be determined and recorded at Visit 2, Visit 4, Visit 5 and Visit 6.

The assessment is performed according to the current standards (Tager et al., 2014) and will be provided as a separate manual to all sites. In brief – patients are instructed to walk down a long corridor at their own pace, attempting to cover as much distance as possible within 6 minutes. At the end of the 6 minute duration, the walked distance is calculated and recorded along with the symptoms experienced by the patient. It is crucial that patients are allowed to

[redacted]

rest, before the test is performed – therefore the 6-minute walking test should be done as the last assessment at the respective visits.

6.4.3 Patient Global Assessment (PGA)

The Patient Global Assessment(PGA) is a self-reported tool to assess the patients' subjective rating of their disease activity widely used in HF research and other indications. It has been shown that the PGA responses of CHF patients correlate the patients' functional capacity assessed by means of the 6-minute walk test (Cooper et al., 2016).

The patients are asked to report functioning or response to an intervention by rating their current condition compared to their pre-intervention condition on a numerical scale:

1) much improved 2) moderately improved 3) a little improved 4) unchanged 5) a little worse 6) moderately worse or 7) much worse.

This self-assessment will be completed by the patients in a quiet environment, before any study assessment or drug dispensing at Visit 4, Visit 5 and Visit 6.

6.4.6 Appropriateness of efficacy assessments

Actigraphy represents a state of the art, objective measure of human physical activity. Provided the accelerometry device is worn continuously (or only with minor interruptions) the data collected provide the most objective and accurate measure of patients' activity and sleep profiles. The raw accelerometry data are subject to integration by means of dedicated software which ensures data integrity and quality. The software employs algorithms to derive objective actigraphy measures (e.g. activity counts per minute) from the raw accelerometry data which in turn are used to derive the actigraphy-based study endpoints. Actigraphy-based endpoints reflect the patients' physical activity and behavior in their familiar environment. In addition, the 6-minute walking test is a frequently used functional test that allows for the evaluation of the patients' submaximal exercise capacity and thus provides information on the patients'

physical activity tolerance. [redacted]

6.5 Safety

The sponsor may request additional information on specific AEs or laboratory events of interest and may make requests to perform additional diagnostic tests to further assess the safety profile of sacubitril/valsartan. Such information may include diagnostic procedure reports, discharge summaries, autopsy reports and other relevant information that may help in assessing the reported adverse event. All such additional information must be de-identified prior collection by Novartis or its representatives.

6.5.1 Physical examination

A complete physical examination will be performed at Visit 1. A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A short physical exam will include the examination of general appearance and vital signs (blood pressure (BP) and pulse). A short physical exam will be performed at all visits starting from visit 2 except where a complete physical examination is required (Visit 1, see above).

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after signing the informed consent form which meet the definition of an AE must be recorded on the Adverse Event section of the CRF.

6.5.2 Vital signs

Vital signs will be assessed at every visit and include BP and pulse measurements. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using a standard sphygmomanometer with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. Guidelines for BP-management are provided in Appendix 5.

6.5.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at visit 1; weight will be measured again at the final visit.

[redacted]

6.5.4 Laboratory and diagnostic evaluations

For patient safety the following laboratory parameters should be monitored at the screening visit (Visit 1) and before randomization (Visit 2), as well as throughout the up-titration of study drug and as per discretion of the investigator.

- Potassium
- Creatinine and eGFR
- AST and ALT

These laboratory evaluations are standard safety parameters in the context of prescribing ACEI, ARBs or sacubitril/valsartan. They will be performed by the local lab and should be entered into the patient's source data and into the clinical study database.

Clinically notable laboratory findings are defined in Appendix1, Appendix 2, Appendix 3 and Appendix 4.

A standard 12-lead ECG will be performed at screening (Visit 1, unless an ECG performed within the last 3 months is available) to assess the eligibility of patients regarding inclusion and exclusion criteria. Interpretation of the tracing must be made by a qualified physician. Each ECG tracing should be labeled with the study number, patient number, and date and kept in the source documents at the study site. Clinically significant abnormalities according to the judgment of the investigator should also be recorded on the relevant medical history/current medical conditions or AE eCRF page.

In addition, if available within the investigator's routine management of HF, any assessment of LVEF, NT-proBNP and hemoglobin during the study can be entered into the study database, but is not stipulated by the protocol.

6.5.5 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have urine pregnancy testing at Visit 2 prior to randomization and at the end of study visit. In case, urine pregnancy test is positive, results are to be confirmed by local serum pregnancy tests. Additional pregnancy testing might be performed if and as requested by local requirements.

6.5.6 Appropriateness of safety measurements

The safety assessments selected are standard for this indication and patient population.

[redacted]

[redacted]

7 Safety monitoring

7.1 Adverse events

An AE is any untoward medical occurrence (e.g., any unfavorable and unintended sign, including abnormal laboratory findings, symptom or disease) in a 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 patient at each visit during the study. AEs also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual

patient 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:

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment
  - "No Relationship to study treatment or other investigational treatment" or
  - "Relationship to study treatment" or
  - "Relationship to other investigational treatment" or
  - "Relationship to both study treatment and other investigational treatment or indistinguishable"
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding investigational treatment; All AEs 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
  - patient hospitalized/patient'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 patient informed consent and should be discussed with the patient 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 patient.

[redacted]

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient'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 patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient 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 patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to 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 patient 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.

[redacted]

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period 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,* 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 patient 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 Liver safety monitoring

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

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter

[redacted]

- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 14-1 of Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 14-1 of Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 14-2 of Appendix 2.

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation.

Repeat laboratory tests must be entered on the appropriate unscheduled local laboratory CRF page.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed must be recorded on appropriate CRF pages, including the liver event overview CRF pages.

7.4 Renal safety monitoring

To ensure patient safety, a standardized process for identification, monitoring and evaluation of renal dysfunction is summarized in Appendix 3.

7.5 Serum potassium safety monitoring

To ensure patient safety, a standardized process for identification, monitoring and evaluation of hyperkaliemia is summarized in Appendix 4.

7.6 Hypotension monitoring

To ensure patient safety, a standardized process for identification, monitoring and evaluation of hypotension is summarized in Appendix 5.

[redacted]

7.7 Angioedema monitoring

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. Bradykinin has been implicated as the putative mediator. Thus, medications that raise levels of endogenous bradykinin (such as ACEI and NEP inhibitors) may result in this potentially dangerous effect. It is important that the investigator pays special attention to any swelling or edema that may resemble angioedema angioedema-like events that may be reported by the patient.

If angioedema occurs, study drug should be immediately discontinued and appropriate therapy and monitoring should be provided by the investigator until complete and sustained resolution of signs and symptoms have occurred. After discontinuation of study drug due to an angioedema, study drug must not be re-administered.

7.8 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be 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

7.9 Pregnancy reporting

To ensure patient 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.

[redacted]

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.

7.10 Prospective suicidality assessment

Not applicable.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the 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 CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients/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 using fully validated software that conforms to US CFR 21Part 11

[redacted]

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 before transfer of the data to the CRO working on behalf of Novartis. 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 patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff, or a CRO working on behalf of Novartis, review the data entered into the CRFs by investigational 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. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Actigraphy data will be downloaded by the investigator and transferred to a CRO working on behalf of Novartis by means described in the investigator's folder. Raw Data will be processed by the CRO working on behalf of Novartis, by means of appropriate and dedicated computer programs. The processed data will be sent electronically to the clinical data base for analysis.

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

Not required.

[redacted]

8.5 Adjudication Committee

Not required.

9 Data 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.

Summary statistics for continuous variables will include valid N, missing N, mean, standard deviation, minimum, median, maximum. Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies.

Details of the planned statistical analysis will be described in a separate statistical analysis plan (SAP), which will be finalized prior to data base closure. All analyses will be carried out by means of the SAS® package (version 9.2 or higher).

9.1 Analysis sets

Three analysis data sets will be defined. The safety data set (SAF) consists of all patients who have received the study medication at least once. The full analysis set (FAS) comprises all patients of the safety data set who provide the baseline value and any post-baseline value of at least one primary endpoint (6-minute walking test or daily non-sedentary daytime activity). The per-protocol (PP) data set includes all patients of the FAS who do not have any major deviations from the protocol. Such deviations will be defined in the Data Validation Plan or similar document and in the protocol of the blind data review without knowledge of the treatment group assignment.

9.2 Patient demographics and other baseline characteristics

Summary statistics will be presented for continuous demographic and baseline characteristics, including age, age groups (<65 years vs. ≥ 65 years), sex, race, ethnicity, source of patients' referral, the patients' living conditions, smoking status, relevant medical history/current medical condition, previous drug/non-drug therapy of HF, concomitant medication and non-drug therapy. Furthermore, weight, height, body mass index (BMI) and NYHA class will be provided. BMI will be calculated as weight (kg) / height² (m^2) from the collected height and weight at the screening Visit 1.

Variables will be summarized according to the analyses for continuous and categorical data described in Section 9 above. The analysis will be performed for all patients in the FAS and additionally stratified by treatment group.

9.3 Treatments

The duration of exposure to study drug will be summarized for all patients treated in the SAF, separately by treatment group. Additionally, the number and percentage of patients will be summarized by treatment group for duration category. Compliance will be calculated in

[redacted]

percent as the number of tablets administered divided by the number of tablets scheduled according to the protocol.

Prior and concomitant medications and non-drug therapies will be summarized by therapeutic class, preferred term, and treatment group for the SAF. Prior medications are defined as treatments taken and stopped prior to first dose of study drug. Any medication given at least once between the day of first dose of study drug and the last day of study will be a concomitant medication, including those which were started pre-Baseline and continued into the treatment period.

9.4 Analysis of the primary variable(s)

9.4.1 Variable(s)

There are two primary variables. The physical activity primary variable is the change in walking distance in meters from baseline to visit 6 as assessed by the 6 minute walk test. The actigraphy primary variable is the change from baseline to 'end of study' in mean daily non-sedentary daytime activity (defined as ≥178.50 counts per minute) as calculated by the MotionWatch 8 accelerometer device. Baseline is defined as the average min per day in non-sedentary daytime activity over 2 weeks (week -2 to week 0) prior to randomization and 'end of study' is defined as the average minutes per day in non-sedentary daytime activity between week 10 to week 12.

The aim of the primary analysis of this study is to assess differences between sacubitril/valsartan and enalapril patients with respect to the primary endpoint in the FAS.

9.4.2 Statistical model, hypothesis, and method of analysis

6-minute walk test: The primary hypothesis to be rejected is that the change in 6-minute walk test between baseline and 'end of study' under sacubitril/valsartan is equal to the change under enalapril.

Non-sedentary daytime activity: The primary hypothesis to be rejected is that the change in weighted mean non-sedentary daytime activity between baseline and 'end of study' under sacubitril/valsartan is equal to the change under enalapril. Both analyses will be performed in the same way, let μj denote the expected change in 6-minute walk test or mean daily non-sedentary daytime activity in group j, j=0,1 where

- 0 corresponds to treatment with sacubitril/valsartan and
- 1 corresponds to treatment with enalapril.

The following hypothesis will be tested:

H0: $\mu 0 = \mu 1$ vs. H1: $\mu 0 \neq \mu 1$

The primary efficacy variable will be analyzed using analysis of covariance (ANCOVA), with factors treatment and baseline NYHA class (NYHA II vs. III/IV) and the baseline value as covariates. The two-sided 95%-confidence interval and the corresponding p-value for the between-group difference of the adjusted means (least square means) of both treatment groups will be provided from the ANCOVA model.

[redacted]

Confirmatory testing, i.e. the primary analysis of the primary variable, will be carried out for the FAS. The level of significance will be set to $\alpha = 0.05$ (two-sided).

9.4.3 Handling of missing values/censoring/discontinuations

For patients who do not have the baseline values or patients who drop out prematurely and/or do not have a valid measurement in mean daily non-sedentary daytime activity between weeks 10-12, a Multiple Imputation (MI) method will be used for the primary analysis.

In case of qualitative (e.g., increased level of non-sedentary daytime physical activity) or semi-quantitative (e.g., PGA) efficacy variables, missing Week 12 values of patients previously dropped out due to hospitalization or death will be substituted by the worst value possible for the respective variable (e.g., increased level of non-sedentary daytime physical activity=”No”, PGA=”much worse”).

9.4.4 Sensitivity analyses

In addition to the primary analysis in non-sedentary daytime activity, the variable will also be analyzed using the same analysis model in the PP population with MI and without multiple imputation as supportive. Furthermore, the analysis of the primary variable will be repeated in the FAS population with MI of missing values described in Section 9.4.3.

Besides, the last-observation-carried-forward principle (LOCF) imputation method for non-sedentary daytime activity will be performed as a sensitivity analysis. For patients who drop out prematurely and/or do not have a valid measurement in mean daily non-sedentary daytime activity between weeks 10-12, the last available value of non- sedentary daytime activity over two weeks under treatment will be used for the primary analysis.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

For the secondary variable is the proportion of patients with increased level of non-sedentary daytime physical activity at ‘end of study’ compared to baseline. It will be analyzed by applying a logistic regression model with factors treatment and baseline NYHA class (NYHA II vs. III/IV) and the baseline value as further covariate. The Odds Ratio for the factor treatment and its 95%-confidence interval will be given. The analysis of this secondary variable will be performed in the FAS (with and without imputation of missing values described in Section 9.4.3.) and additionally in the PP population with and without imputation of missing values.

All other secondary efficacy variables will be analyzed descriptively using the statistics for continuous and categorical data described in Section 9 above. Additionally, two-sided tests of significance (with $\alpha = 0.05$) between the two treatment groups will be performed for all secondary endpoints, using appropriate testing procedures. Details to those statistical testing procedures will be defined in the SAP.

[redacted]

All statistical tests of secondary efficacy variables will be on an exploratory basis. Therefore, no multiple testing strategy will apply for these tests

9.5.2 Safety variables

All safety evaluations will be performed in the Safety set.

9.5.2.1 Adverse events

Treatment emergent adverse events (events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized. Only primary paths within MedDRA will be considered for AE reporting.

AEs will be summarized by presenting, for each treatment group, the number and percentage of subjects

- having any AE,
- having an AE in each primary system organ class and
- having each individual AE (preferred term).

Summaries will also be presented for AEs by severity and for study treatment related AEs. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

Separate summaries will be provided for death, serious adverse event, adverse events leading to discontinuation and adverse events leading to dose adjustment (including study treatment discontinuation).

9.5.2.2 Laboratory data

Laboratory data will be summarized by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (mean, medians, standard deviations, ranges) and by the flagging of notable values in data listings.

9.5.2.3 Vital signs

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for subjects with both baseline and post-baseline values. All information collected will be listed by subject and abnormal values be flagged.

9.5.3 Resource utilization

Not applicable.

[redacted]

9.5.4 Pharmacokinetics Not applicable.

9.5.5 DNA

Not applicable.

9.5.6 Biomarkers

Not applicable.

9.5.7 PK/PD Not applicable.

[redacted]

9.7 Interim analyses

Not applicable.

9.8 Sample size calculation

There are no published data on a possible effect of a drug intervention on physical activity in HFrEF patients. However, Alosco and colleagues observed patients with HF over a period of 12 weeks and reported activity levels at baseline and after 12 months using a similar accelerometry device (Alosco et al., 2015). The mean activity time in light intensity was 188 min/day (SD = 56) at baseline and 183 min/day (SD = 58) after 12 weeks. The corresponding values for activity in moderate to vigorous intensity were 46 min/day (SD = 35) at baseline and 41 min/day (SD = 30) after 12 weeks. From these data an average of 234 min/day at baseline and 224 min/day after 12 weeks can be concluded for the non-sedentary daily activity time. The observed standard deviations for sedentary daily activity time were 76 min/day (baseline) and 63 min/day (month 12), respectively. From these values the standard deviation for non-sedentary activity time (which is approximately the same as for sedentary activity time) is estimated as SD = 70 min/day for both time points.

[redacted]

For the present study we assume a mean baseline value of 200 to 230 min/day for both treatment groups. If treatment with sacubitril/valsartan leads to an improvement which is at least 20 min/day higher than the changes under enalapril, this is considered as clinically relevant.

The standard deviation for the changes from baseline is expected not to be larger than the standard deviations at the two respective visits (corresponding to a correlation coefficient of 0.5 between the values at baseline and at week 12 to 14). Accordingly, the standard deviation for the primary endpoint is estimated as SD = 70 min/day for both treatment groups.

Planning a two-sided test (using the t-test model with $\alpha = 5\%$ and 90% power at $\Delta = 20$ min/day) results in 259 patients per treatment group (nQuery Advisor® 7.0). In order to account for non-eligible patients, it is planned to recruit 300 patients per treatment arm, i.e. 600 patients in total.

With respect to the primary endpoint "change in 6-minute walk test between baseline and weeks 4, 8 and 12", the following sample size considerations apply: From Täger et al. and Shoemaker et al., we deduce a minimal important difference of 35 meters at week 12 and a standard deviation of 114 meters (Tager et al., 2014). Planning a two-sided test with $\alpha = 0.05$ and 90% power for a group difference of 35 meters leads to a sample size of 224 patients per group, which is covered by the planned patient numbers.

After defining the primary hypotheses H1 and H2, to control the familywise error rate at level 5%, the Hochberg procedure will be used to test the primary hypotheses. It will reject both H1 and H2, if both of them are significant at level 5% simultaneously. Otherwise, it will reject H1 if it is significant at level $\alpha/2$, or reject H2 if it is significant at level $\alpha/2$.

Table 9-1 Power of the study considering both the end-points – Considering 259 subjects in each arm

Correlation between the two end-points	Power to reject H1	Power to reject H2	Power to reject any of H1 and H2	Power to reject both of H1 and H2
0	89.7%	93%	98.5%	84.4%
0.2	89.5%	93%	97.6%	85%
0.4	89.4%	93%	96.5%	85.7%
0.5	89.3%	93%	96%	86%
For power calculations, H1 is based on accelerometry data end-point while H2 is based on the 6 minutes walking test end-point.				

Table 9-2 Power of the study considering both the end-points – Considering 300 subjects in each arm

Correlation between the two end-points	Power to reject H1	Power to reject H2	Power to reject any of H1 and H2	Power to reject both of H1 and H2
0	93.6%	96.2%	99.4%	90.4%
0.2	93.5%	96%	99%	90.6%

[redacted]

0.4	93.4%	96%	98.2%	91%
0.5	93.3%	95.8%	97.8%	91.3%
For power calculations, H1 is based on accelerometry data end-point while H2 is based on the 6 minutes walking test end-point.				

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 patients/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 patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient 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 patient 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 patient 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

[redacted]

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 patients/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 patients/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 patient 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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To be provided upon request

13 Appendix 1: Clinically notable laboratory values

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

Hemoglobin	> 50 % increase, > 20 % decrease
ALT	> 150 % increase
AST	> 150 % increase
Creatinine	> 50 % increase
Potassium	> 20 % increase, > 20 % decrease

[redacted]

14 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 14-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

Table 14-2 Follow Up Requirements for Liver Events and Laboratory Triggers

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

[redacted]

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

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

[redacted]

15 Appendix 3: Specific Renal Alert Criteria and Actions

Table 15-1 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 patient hospitalization /specialized treatment
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient 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.	

Please also refer to Appendix 6.

16 Appendix 4: Treatment guidelines for hyperkaliemia (serum potassium greater than or equal to 5.5 mmol/L)

General principles

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

Any patient with a serum potassium ≥ 5.5 mmol/L after enrollment into the study requires regular, repeated checks of potassium concentration (beyond that prescribed in the protocol) until it is clear that the potassium concentration is stable and not rising into the range of concern (≥ 5.5 and < 6.0 mmol/L) or potential danger (≥ 6.0 mmol/L).

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

Corrective action for management of hyperkalemia

Serum potassium greater than 5.5 and lower than 6.0 mmol/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)

[redacted]

  - 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 trimethoprim/sulfamethoxazole fixed combinations
  - 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 mmol/L, regularly monitor serum potassium levels to ensure stability (suggested once monthly).
- Consider down-titration of study medication, according to investigator's medical judgment.
- Consider down-titration or temporarily discontinue study drug according to investigator medical judgment.
- Repeat serum potassium measurement after 2-3 days
- If serum potassium < 5.5 mmol/L, consider resumption of study drug at lower dose with repeat potassium within 5 days

Serum potassium greater than or equal to 6.0 mmol/L

- Immediately discontinue study drug
- Confirm potassium concentration in a non-hemolyzed sample
- Urgently evaluate patient and treat hyperkalemia as clinically indicated
- Apply all measures outlined for serum potassium ≥ 5.5 and < 6.0 mmol/L

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

[redacted]

17 Appendix 5: 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
   c. If hypotension persists, the study drug should be down-titrated or even temporarily withdrawn. The dose re-challenge and medications adjust guidelines described in Section 5.5.5 should be adhered to as much as possible.

18 Appendix 6: Guidelines for the management of renal dysfunction

General principles:

Glomerular filtration rate in HF patients 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 patients after study drug administration. These recommendations have been developed to guide the investigators in managing patients with renal dysfunction after randomization.

Two types of response to serum creatinine increase are described:

Surveillance situation

If, at any time after randomization, eGFR decreases by ≥ 25% from baseline (Visit 2) (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 serum creatinine levels
- Volume decrease, including that resulting from excessive dosing of diuretics
- Urinary infection
- Urinary tract obstruction
- Study medication

[redacted]

Action situation

If a patient eGFR decreases by ≥ 40% from baseline (Visit 2) (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.

[redacted]