CLINICAL STUDY PROTOCOL

Controlled trial on the short-term effects of sacubitril/valsartan therapy on cardiac oxygen consumption and efficiency of cardiac work in patients with NYHA II-III heart failure and reduced systolic function using ^{11}C-acetate positron emission tomography and echocardiography

CLCZ696BFI03 / NCT03300427

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Phase:	IV
EudraCT No:	2017-002113-64
Sponsor:	Novartis Finland Oy
Principal Investigator:	[redacted]
Institute:	[redacted]

The study will be conducted in accordance with GCP.

SIGNATURES

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SYNOPSIS

Name of the Sponsor/Company: Novartis Finland Oy		
Name of the active ingredient: Sacubitril/valsartan		

Study code:
CLCZ696BFI03 (Sponsor) / C605 [redacted], EudraCT 2017-002113-64

Study title:
Controlled trial on the short-term effects of sacubitril/valsartan therapy on cardiac oxygen consumption and efficiency of cardiac work in patients with NYHA II-III heart failure and reduced systolic function using ^{11}C-acetate positron emission tomography and echocardiography

Investigators and study centres:
[redacted] (Principal Investigator), MD, PhD. [redacted], Finland

Development phase:
IV

Objectives:
Primary objective: The primary objective of the study is to evaluate the effects of 6 weeks of stable sacubitril/valsartan therapy, as compared with valsartan therapy, on the efficiency of cardiac work in patients with NYHA II-III heart failure (HF) and reduced systolic function using ^{11}C-acetate and echocardiography.
Exploratory objective: The exploratory objective of the study is to evaluate the effects of 6 weeks of stable sacubitril/valsartan therapy, as compared with valsartan therapy, on myocardial oxygen consumption and cardiac and systemic hemodynamics.

Methodology:
This is a phase IV, prospective, randomized, double-blind, double-dummy, parallel-group study performed at a single center. The subjects enrolled into the study will be patients with chronic HF, NYHA II-III symptoms and reduced ejection fraction (EF) who fulfill all of the inclusion criteria and none of the exclusion criteria. No more than 50% of the study subjects are allowed to have diabetes. The study will have two treatment arms, the sacubitril/valsartan treatment arm and the valsartan treatment arm, and the subjects will be randomized into these arms in a 1:1 ratio. The study will be performed in a double-blinded manner in regards to the treatment. As the sacubitril/valsartan and valsartan tablets are not similar in appearance, the study will be performed in a double-dummy manner in order to maintain blinding. Regardless of the treatment arm a subject is in, the study drug will be up-titrated to the highest tolerated dose level during the scheduled study visits. The different strengths of the two study drugs are not identical in appearance so the possible dose modification(s) during the treatment period cannot be performed in a blinded manner. The subjects will start on valsartan (80 mg twice a day [BID] or 160 mg twice a day) or sacubitril/valsartan (100 mg BID) dose and there will be only one scheduled up-titration visit after the randomization. If clinically indicated, dose modification (up- or down-titration) will be allowed once after the randomization outside the scheduled study visits. In order to be eligible for the final study assessments on visit 3 (i.e. the ^{11}C-acetate positron emission tomography [PET] scan and echocardiography), the subjects have to be on a stable dose for at least 6 weeks on one of the following treatment options: valsartan 80 mg BID or 160 mg BID or sacubitril/valsartan 100 mg BID or 200 mg BID.

Study treatment will be dispensed by an unblinded member of the study team during the treatment period.
The total duration of the study is planned to be approximately 14 weeks for each subject, but it may be longer if required for scheduling purposes. During the study, the subjects will have 5-6 study visits. Two of these visits, screening visit 2 and visit 2, may performed as a remote visit (i.e. telephone contact), if deemed sufficient by the investigator. In addition, unscheduled visits may occur at any time, if considered necessary for subject safety. The study includes a screening/run-in period (up to 6 weeks) and a treatment period (approximately 8 weeks). Both the screening/run-in and the treatment period may be longer, if necessary. Efficacy assessments, i.e. ^{11}C-acetate PET-scan and echocardiography, will be performed twice during the study. The first assessments will be done at the baseline visit, after the subject has been on a stable valsartan treatment for a minimum of 4 weeks, and then repeated at the last visit, when the subject has been on a stable sacubitril/valsartan or valsartan treatment for a minimum of 6 weeks. Subject safety will be monitored throughout the study by evaluating the subject's clinical status, blood pressure (BP), heart rate (HR) and safety laboratory assessments. Specific safety-related withdrawal criteria are given in section 5.8.

Sample size:
The planned number of enrolled study subjects is 60 (30 subjects/treatment arm). The aim is that at least 27 subjects/treatment arm finish the study according to the protocol. If discontinuations occur, the need of recruiting additional subjects to reach the targeted total number of subjects will be considered and carried out as appropriate. Thus, in case of discontinuations during the study, the number of enrolled study subjects may be larger than 60.

Main eligibility criteria:
Patients with 40-80 years of age and chronic HF with reduced EF (left ventricle EF 25-35%) and NYHA class II-III symptoms; estimated glomerular filtration rate (eGFR) ≥ 45 ml/min; serum potassium <5.2 mmol/l and creatinine <1.5 x ULN (upper limit of normal) at the screening visits; systolic BP 110-160 mmHg at the randomization visit; optimal standard HF therapy according to European Society of Cardiology (ESC) guidelines at a stable dose for at least 4 weeks before the screening visit. The subjects must fulfill all of the inclusion criteria and none of the exclusion criteria.

Investigational drug, dose and mode of administration:
The investigational drug will be sacubitril/valsartan (Entresto™). It will be taken orally BID. Two strengths will be available for use after randomization, 49 mg sacubitril/51 mg valsartan and 97 mg sacubitril/103 mg valsartan. After randomization, subjects will receive either sacubitril/valsartan 100 mg BID or valsartan 80 mg BID or 160 mg BID (depending on the screening/run-in dose). The dose will be then up-titrated to the highest tolerated dose (or maintained at the starting dose level, if up-titration is not possible). In case of sacubitril/valsartan, the dose will be either up-titrated to 200 mg BID or maintained at 100 mg BID. In order to be eligible for the final assessments, the subject has to tolerate the 100 mg BID dose at the minimum (i.e. subjects who do not tolerate the change to sacubitril/valsartan 100 mg BID will be withdrawn from the study).

Comparative drug(s)/placebo, dose and mode of administration:
Valsartan 80 mg and 160 mg tablets will be used as comparative drugs, taken orally BID. At screening visit 1, the subjects will be switched to valsartan treatment that will replace their previously used angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II

receptor blocker (ARB) treatment during the screening/run-in period. The starting dose of valsartan is 80 mg BID or if a subject is already on a dose of 160 mg BID or equivalent the dose will be maintained on that level. Subjects will be maintained at a stable dose of 80 mg BID or 160 mg BID of valsartan for at least 4 weeks before randomization. After randomization, subjects that were on 80 mg BID valsartan dose during the run-in will receive either sacubitril/valsartan 100 mg BID or valsartan 80 mg BID. Subjects that were on 160 mg BID valsartan during the run-in will be randomized to either valsartan 160 mg BID or sacubitril/valsartan 100 mg BID. The dose in both treatment arms will be then up-titrated to the highest tolerated dose (or maintained at the starting dose level, if up-titration is not possible). In order to be eligible for the final assessments, the subject has to tolerate the 80 mg BID dose of valsartan at the minimum.

Duration of treatment:

The subjects will receive valsartan treatment during the screening/run-in period. The screening/run-in period can last for up to 6 weeks (may be longer, if needed) and the valsartan dose has to be stable for at least 4 weeks prior to randomization. After randomization, subjects will receive study treatment (either valsartan or sacubitril/valsartan) for approximately 8 weeks; during the first 2 weeks, the dose of the study drug will be up-titrated to the highest tolerated dose level (or the starting dose will be maintained, if up-titration is not possible on clinical bases or if the subject is already on the highest dose level), and then the highest tolerated dose will be administered for 6 weeks at a stable dose prior to the final efficacy assessments.

Assessments:

Efficacy assessments: ^{11}C-acetate PET scan, echocardiography and biomarkers

In order to assess cardiac efficiency and hemodynamics, PET imaging and echocardiography will be performed before randomization (after a minimum of 4 weeks on stable dose of 80 mg BID or 160 mg BID of valsartan) and repeated after 6 weeks on a stable dose of either 80 mg BID or 160 mg BID of valsartan or 100 mg BID or 200 mg BID of sacubitril/valsartan.

^{11}C-acetate PET: Myocardial resting perfusion and oxygen consumption will be evaluated by ^{11}C-acetate PET as tracer uptake (k_1) and a mono-exponential clearance rate of ^{11}C-acetate (k_{mono}). Efficiency of left ventricle (LV) mechanical work will be calculated as follows: Efficiency = (LV work/gram of tissue) / oxygen consumption.

Echocardiography: Comprehensive echocardiographic evaluation of cardiac structure, systolic and diastolic function will be performed using 2D and 3D imaging, strain imaging and Doppler. LV mechanical work will be calculated as follows: LV work/gram of tissue= (SBP x SV x HR) / LV mass; where SBP is systolic blood pressure, SV is stroke volume and HR is heart rate.

Biomarkers: Biomarkers (N-terminal prohormone brain natriuretic peptide [NT-proBNP], hs-troponin and creatinine) will be measured to understand the possible mechanisms of the potential changes in myocardial efficiency.

Safety: Seated BP and HR will be measured at all site visits for safety assessment. BP and HR will be monitored also during the imaging sessions. All subjects will undergo blood laboratory tests, including serum potassium and creatinine, during the screening/run-in period on screening visits 1 and 2. The same laboratory assessments will be performed during the treatment period on visits 1-3, and also on unscheduled visits, if clinically indicated. If necessary to assess subject safety, more laboratory tests may be performed at any visit.

The decision to modify (up- or down-titrate) the dose level of a subject's study drug (either valsartan or sacubitril/valsartan) during the study may be done without the knowledge of the laboratory results; however, the results must be available and reviewed as soon as possible to ensure subject safety. Adverse events (AEs) and changes in concomitant medication(s) will be reported and documented throughout the study.

Statistical methods:

The study hypothesis is that short-term therapy with sacubitril/valsartan added on standard HF therapy improves cardiac efficiency in patients with systolic HF. Analysis of covariance (ANCOVA) will be used for statistical analysis, when appropriate. Other statistical analyses may also be implemented, as described in the statistical analysis plan (SAP).

Efficacy: The difference in the primary (cardiac efficiency) and exploratory efficacy parameters will be evaluated by comparing change from baseline at visit 3 between treatment groups. Change from baseline will be analysed using an ANCOVA, adjusting for treatment, strata, and baseline. From this model the treatment difference will be estimated with a 95% confidence interval (CI). In addition, treatment by stratification interaction analyses will be performed for the primary efficacy parameters in order to estimate within stratification group differences.

Safety: AEs reported during the study will be classified by system organ class (SOC) and preferred terms (PT) using the MedDRA coding system. The number and proportion (%) of subjects' AEs will be presented by treatment and dose level and the severity and causality will be tabulated with subject and event counts. Systolic and diastolic BP and HR and laboratory safety variables and their changes from the baseline values will be evaluated and summarized using descriptive statistics by treatment and dose level. The laboratory values tabulated as low, normal or high according to their reference ranges and clinically significant laboratory abnormalities will be listed.

ABBREVIATIONS AND DEFINITION OF TERMS

ACE	Angiotensin-converting enzyme
ACEI	Angiotensin-converting enzyme inhibitor
ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
ANCOVA	Analysis of covariance
AngII	Angiotensin II
ANP	Atrial natriuretic peptide
ARB	Angiotensin II receptor blocker
ARNI	Angiotensin receptor/neprilysin inhibitor
ATR	Angiotensin receptor
AUC	Area under the concentration-time curve
BID	Twice a day
BP	Blood pressure
CA	Competent authority
cGMP	cyclic Guanosine monophosphate
CI	Confidence interval
C_{max}	Peak plasma concentration
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CV	Cardiovascular
CV%	Coefficient of variation
DM	Data management
DMP	Data management plan
EC	Ethics committee
ECG	Electrocardiogram
(e)CRF	(electronic) Case report form
EDC	Electronic data capture
EF	Ejection fraction
eGFR	estimated Glomerular filtration rate
EMA	European Medicines Agency
EPAR	European public assessment report
ESC	European Society of Cardiology
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
HF	Heart failure
HR	Heart rate
IB	Investigator's Brochure
IC	Informed consent
ICF	Informed consent form
ICH	International Conference on Harmonization
IMP	Investigational medicinal product
ISF	Investigator's study file
iv.	intravenous
LSLV	Last subject last visit
LV	Left ventricle
LVIDD	Left ventricular internal diastolic diameter
LVOT	Left ventricle outflow tract
MedDRA	Medical Dictionary for Regulatory Activities

MRA	Mineralocorticoid receptor antagonists
MR-proANP	Mid-regional pro-atrial natriuretic peptide
NCI	National Coordinating Investigator
NEP	Neutral endopeptidase
NHANES	National Health and Nutrition Examination Survey
NP	Natriuretic peptide
NSAID	Non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal prohormone brain natriuretic peptide
NYHA	New York Heart Association
PET	Positron emission tomography
PPS	Per protocol set
PT	Preferred term
RAAS	Renin-angiotensin-aldosterone system
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SOC	System organ class
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse drug reaction
SV	Stroke volume
SVR	Systemic vascular resistance
TCA	Tricarboxylic acid cycle
TMF	Trial master file
ULN	Upper limit of normal
WHO DD	World Health Organization Drug Dictionary

1 AMENDMENTS AND UPDATES

Table 1 Substantial study protocol amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1.1	04JAN2019	Synopsis, 4.3, 6.7, 7.1, 7.2	The possibility to perform screening visit 2 and visit 2 as remote visits	Reduce the number of site visits and thus the burden caused by the study on the subjects
1.5	24JUNE2020	Synopsis, 5.3	Changing the upper age limit of the eligible patients from 75 to 80 years	Improvement of recruitment rate. Several eligible study candidates have been aged between 75 and 80 years.

1.1 The possibility to perform screening visit 2 and visit 2 as remote visits

Date/version of change: 04JAN2019, protocol version 2.0 (amendment 1)

Section: Synopsis; 4.3 General study outline; 6.7 Procedures for monitoring subject compliance; 7.1. Screening/run-in period; 7.2 Treatment period;

Was: NA; updates to the protocol were done throughout the protocol text to reflect the changes described in Item 1.1.

Should be: With protocol amendment 1, the possibility to perform screening visit 2 and visit 2 as remote visits (with the exception of safety laboratory assessments) was added. As a result of this, the number of visits during the study altogether and during the treatment period was updated. Updates were made also to the general study design (Figure 1.) and general study outline (Table 3.).

Reason: In order to reduce the number of site visits and thus the burden caused by the study on the subjects, screening visit 2 during the screening/run-in period and visit 2 during the treatment period may be performed as remote visits, if deemed sufficient by the investigator. It is of note that even if these visits are performed as remote visits, the protocol-specified safety laboratory tests have to be performed for each visit to ensure subject safety. Aside from the laboratory tests, other protocol-specified assessments for these visits may be performed remotely (e.g. adverse event and concomitant medication check) or omitted altogether (e.g. blood pressure measurement at site). This change, by reducing subject burden, is expected to have a favorable impact on subject recruitment and retention. Subject safety is not expected to be affected by this amendment as laboratory tests are still performed at each visit and the decision of remote/site visits is done by the investigator based on the laboratory results and overall clinical status of the subject. Subjects will be contacted by the study personnel via telephone or other method if the screening visit 2 and/or visit 2 are performed remotely so the subject will have an opportunity to report any subjective feelings/symptoms and ask questions, if necessary.

1.2 Safety blood samples may be collected 1-2 business day(s) before the scheduled study visits

Date/version of change: 04JAN2019, protocol version 2.0 (amendment 1)

Section: 4.3 General study outline; 7.2 Treatment period; 8.3.3 Laboratory safety assessments

Was: NA; new text added to serve as clarification.

Should be: It was added that safety blood samples may be collected 1-2 business day(s) before the scheduled study visits (with the exception of screening visit 1).

Reason: This update was made to clarify the timing of safety blood samples. The timing of safety blood samples was not specified clearly in the previous protocol version (final version 1.0, 28Aug2017). With this clarification, the protocol text is now in line with the normal procedures of the study site and with the intent of the protocol.

1.3 Primary endpoint clarification

Date/version of change: 04JAN2019, protocol version 2.0 (amendment 1)

Section: 3.1 Primary objective and endpoint

Was: NA, additional text added to serve as clarification.
Should be: Clarification on how the difference in cardiac efficiency will be evaluated.

Reason: This update was made to clarify the primary endpoint of the study. The primary endpoint has not changed. The primary endpoint was not clearly stated in the previous version of the protocol (final version 1.0, 28Aug2017). With this clarification, the protocol text is now in line with how this calculation is described elsewhere in the protocol (section 9.2.6 Analysis of efficacy variables).

1.4 Physical examination clarification

Date/version of change: 04JAN2019, protocol version 2.0 (amendment 1)

Section: Table 3, 8.3.1 Physical examination

Was: NA, new text added to serve as clarification

Should be: The procedure of the physical examination, i.e. examination of general appearance, as well as the cardio-vascular system as seen relevant by the investigator, for example lungs, heart and extremities, as well how this is reported, i.e. in the source documentation at site, has been added.

Reason: This update was made to clarify the procedure of the physical examination, which was not clearly stated in the previous version of the protocol (final version 1.0, 28Aug2017). With this clarification, the protocol text is now in line with the normal procedures of the study site and with the intent of the protocol.

In addition to the above mentioned changes, typographical errors, table and section numbers were also corrected in the protocol text.

1.5 Change of the inclusion criteria: the upper age limit of the eligible patients from 75 to 80 years

Date/version of change: 24JUNE2020, protocol version 3.0 (amendment 2)

Section: Synopsis, 5.3 Inclusion criteria

Was: Age limits in the Inclusion criteria were ≥40 to ≤75

Should be: The upper age limit was changed throughout the protocol to ≤80

Reason: As heart failure is a disease of the elderly, the site has noticed that many of the patients fulfill the other inclusion criteria but are aged between 75 and 80 years. The investigators estimate that incresing the upper age limit of eligible patients to 80 years will decrease the recruitment time up to 4 months.

2 INTRODUCTION

2.1 Background

Heart failure (HF) is a clinical syndrome characterized by typical signs and symptoms caused by structural and/or functional cardiac abnormality and resulting in reduced cardiac output and/or elevated intracardiac pressures at rest or during stress. According to the European Society of Cardiology (ESC) guidelines published in 2016, the prevalence of HF is approximately 1–2% of the adult population in developed countries, rising to ≥10% among people >70 years of age (Ponikowski 2016, Mosterd 2007, Redfield 2003, Ceia 2002). Based on data from National Health and Nutrition Examination Survey (NHANES) 2009 to 2012, an estimated 5.7 million Americans ≥20 years of age suffer from HF and projections show that the prevalence of HF will increase 46% from 2012 to 2030, resulting in > 8 million people ≥18 years of age with HF. In the USA, each year more than 550,000 new HF cases are diagnosed. Data from the Framingham Heart Study indicate that at the age of 40 years, remaining lifetime risk of developing HF for both men and women is 1 in 5, while at 80 years of age, the remaining lifetime risk for development of new HF remains at 20% even with the shorter life expectancy. (Mozaffarian 2015, Hunt 2009). In the Rotterdam Heart Study, the lifetime risk of HF at the age of 55 was 33% for men and 29% for women (Bleumink 2004). The etiology of HF is diverse and may include different cardiovascular (CV) and/or non-cardiovascular pathologies (e.g. ischemic heart disease, toxic, metabolic and inflammatory damage to the heart).

The symptoms of HF are most widely graded according to the New York Heart Association (NYHA) functional classification that is used to describe the severity of symptoms and exercise intolerance (The Criteria Committee of the New York Heart Association. (1994). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. (9th ed.). Boston: Little, Brown & Co. pp. 253–256.). The NYHA classes and the associated symptoms are presented in Table 2 below.

Table 2. NYHA classes and associated symptoms

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

The diagnosis of HF includes evaluation of cardiac function by patient interview and examination, laboratory tests and different imaging modalities. The typical signs and symptoms of HF include e.g. breathlessness, ankle swelling, reduced exercise tolerance and fatigue, elevated jugular venous pressure, pulmonary crackles, gallop rhythm and peripheral oedema. The plasma concentration of natriuretic peptides (NPs) is usually used as an initial diagnostic test in HF. Electrocardiogram (ECG) is also often recorded and an abnormal ECG increases the likelihood of the diagnosis of HF, even though ECG has low specificity (van Riet 2014, Kelder 2011, Davie 1996, Thomas 2002). Some abnormalities on the ECG however may provide information on etiology (e.g. myocardial infarction) and indications for therapy (e.g. anticoagulation for atrial fibrillation, need for a pacemaker).

Among the imaging modalities, echocardiography is the most useful and widely available test in patients with suspected HF to establish the diagnosis. It provides immediate information on chamber volumes, ventricular systolic and diastolic function, wall thickness, valve function and pulmonary hypertension (Paulus 2007, Marwick 2010, Dokainish 2011, Kirkpatrick 2007, Nagueh 2011, Caballero 2015, Garbi 2015, Lang 2015, Gimelli 2014, Voigt 2015). This information is crucial in establishing the diagnosis and in determining appropriate treatment. Other cardiac imaging modalities that may help diagnosis or provide information on the etiology, include e.g. chest X-ray, transesophageal echocardiography, stress echocardiography, magnetic resonance imaging, computed tomography (CT), coronary angiography, single-photon emission CT and positron emission tomography (PET). (Ponikowski 2016).

Over the last 30 years, improvements in the treatments and in their implementation have improved survival and reduced the rate of hospitalization in patients with HF with reduced ejection fraction (EF) (Hubers 2016, Maggioni 2013). According to the guidelines for the diagnosis and treatment of acute and chronic heart failure published by the ESC in 2016, the pharmacological treatments indicated in patients with symptomatic (NYHA class II-IV) HF with reduced EF include the following: angiotensin-converting enzyme inhibitor (ACEI), beta-blockers and mineralocorticoid receptor antagonists (MRA). In selected HF patients, also the following treatments may be indicated: diuretics to reduce the signs and symptoms of congestion; angiotensin II receptor blockers (ARB) in patients who do not tolerate ACEI; angiotensin receptor/neprilysin inhibitor (ARNI) to replace ACEI or ARB in patients that are still symptomatic. (Ponikowski 2016). Recent European data (ESC-HF pilot study) demonstrate that 12-month all-cause mortality rates for hospitalized and stable/ambulatory HF patients were 17% and 7%, respectively, and the 12-month hospitalization rates were 44% and 32%, respectively (Maggioni 2013). In patients with HF (both hospitalized and ambulatory), most deaths are due to CV causes, mainly sudden death and worsening HF. All-cause mortality is generally higher in HF with reduced EF than with preserved EF. (Ponikowski 2016, Maggioni 2013, Pocock 2013).

2.2 Valsartan

The following information on the indication and pharmacodynamics and –kinetics of valsartan is based on the European public assessment reports (EPAR) – product information, annex 1.

Valsartan is an orally active, potent and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT1 receptor subtype, which is responsible for the known CV actions of Ang II. Blocking the AT1 receptor prevents sustained activation of the renin-angiotensin-aldosterone system (RAAS) that would result in vasoconstriction, renal sodium and fluid retention, activation of cellular growth and proliferation, and subsequent maladaptive CV remodeling. Valsartan has a much greater affinity (about 20,000 fold) for the AT1 receptor than for the AT2 receptor but the increased plasma levels of Ang II following AT1 receptor blockade may stimulate the unblocked AT2 receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in CV regulation nor does it inhibit the angiotensin converting enzyme (ACE). Therapeutic indications of valsartan include hypertension, recent myocardial infarction and HF. (Burnier 2001, Hubers 2016).

In the Val-HeFT clinical trial valsartan was compared with placebo on morbidity and mortality in over 5000 NYHA class II (62%), III (36%) and IV (2%) HF patients receiving standard therapy. The mean duration of follow-up in this trial was nearly two years and the mean daily dose of valsartan was 254 mg. All-cause mortality was similar (p=not significant) in the valsartan (19.7%) and placebo (19.4%) groups. The primary benefit was a 27.5% (95% confidence interval [CI]: 17 to 37%) reduction in risk for time to first HF hospitalization (13.9% vs. 18.5%). In a subgroup of patients not receiving ACEI at baseline (n=366), the morbidity benefits were the greatest. In this subgroup all-cause mortality was significantly reduced (by 33%, 95% CI: –6% to 58%) with valsartan compared to placebo (17.3% valsartan vs. 27.1% placebo) and the composite mortality and morbidity risk was significantly reduced by 44% (24.9% valsartan vs. 42.5% placebo). In the overall Val-HeFT population, valsartan treated patients showed significant improvement in NYHA class and HF signs and symptoms, including dyspnea, fatigue, oedema and rales, compared to placebo. Patients treated with valsartan had a better quality of life as demonstrated by change in the Minnesota Living with Heart Failure Quality of Life score. EF was also significantly increased and left ventricular internal diastolic diameter (LVIDD) significantly reduced from baseline in valsartan treated patients. (Maggioni 2002, Cohn 2001, Cohn 2000, Cohn 1999).

For HF indication, the recommended starting dose of valsartan is 40 mg BID. Up-titration to 80 mg and 160 mg BID (to the highest dose tolerated by the patient) is usually done at intervals of at least two weeks. The maximum daily dose administered in clinical trials has been 320 mg in divided doses. Valsartan may be administered with other HF therapies.

According to the information given in the EPAR – product information (annex 1) on the pharmacokinetics of valsartan, following oral administration of valsartan alone, peak plasma concentrations (C_{max}) are reached in 2–4 hours. The mean absolute bioavailability of valsartan is approximately 23%. Food decreases exposure (as

measured by the area under concentration-time curve [AUC]) by about 40% and C_{max} by about 50%. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect. AUC and C_{max} values are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day [BID]). Valsartan is highly bound to serum proteins (94–97%), mainly to serum albumin. Valsartan is not biotransformed to a high extent; only about 20% of dose is recovered as metabolites. Valsartan is primarily eliminated by biliary excretion in feces (about 83% of dose) and renally in urine (about 13% of dose), mainly as unchanged drug. No dosage adjustment is required for patients with a creatinine clearance >10 ml/min. The elimination half-life of valsartan is approximately 6 hours. The average time to peak concentration and elimination half-life of valsartan in HF patients are similar to those observed in healthy volunteers. (Burnier 2001).

2.3 Sacubitril/valsartan

The following information on the indication and pharmacodynamics and –kinetics of sacubitril/valsartan is based on the EPAR – product information, annex 1.

Sacubitril/valsartan (LCZ696) is a sodium salt complex that comprises of two active components, sacubitril and valsartan, and is marketed under the name Entresto™. It exhibits the mechanism of action of an ARNI by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and by blocking the AT1 receptor via valsartan. The complementary CV benefits of sacubitril/valsartan in HF patients are attributed to the enhancement of peptides that are degraded by neprilysin, such as NPs, and the simultaneous inhibition of the effects of Ang II. NPs exert their effects by activating membrane-bound guanylyl cyclase-coupled receptors, resulting in increased concentrations of the second messenger cyclic guanosine monophosphate (cGMP), which can result in vasodilation, natriuresis and diuresis, increased glomerular filtration rate (GFR) and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity, and anti-hypertrophic and anti-fibrotic effects. (Hubers 2016, Gu 2010, Volpe 2014). For valsartan's mechanism of action, please refer to Section 2.2.

Sacubitril/valsartan is indicated in adult patients for treatment of symptomatic chronic HF with reduced EF. The pharmacodynamic effects of sacubitril/valsartan were evaluated after single and multiple dose administrations in healthy subjects and in patients with HF, and are consistent with simultaneous neprilysin inhibition and RAAS blockade (Gu 2010). In a 7-day valsartan-controlled study in HF patients with reduced EF, administration of sacubitril/valsartan resulted in an initial increase in natriuresis, increased urine cGMP, and decreased plasma levels of mid-regional pro-atrial natriuretic peptide (MR-proANP) and N-terminal prohormone brain natriuretic peptide (NT-proBNP) compared to valsartan. In a 21-day study in HF patients with reduced EF, sacubitril/valsartan significantly increased urine atrial natriuretic peptide (ANP) and cGMP and plasma cGMP, and decreased plasma NT-proBNP, aldosterone and endothelin 1 compared to baseline. The AT1-receptor was

also blocked as evidenced by increased plasma renin activity and plasma renin concentrations. (Kobalava 2016).

In the large phase III PARADIGM-HF study, sacubitril/valsartan decreased plasma NT-proBNP and increased plasma BNP and urine cGMP compared with enalapril. PARADIGM-HF was a multinational, randomized, double-blind study of over 8400 patients comparing sacubitril/valsartan to enalapril, both given to adult patients with chronic HF, NYHA class II-IV and reduced EF (≤40%, amended later to ≤35%), in addition to standard HF therapy. During the double-blinded period of the study, the subjects received either sacubitril/valsartan 200 mg or enalapril 10 mg BID [sacubitril/valsartan (n=4209); enalapril (n=4233)]. In the study, sacubitril/valsartan was superior to enalapril in reducing the risk of CV death or HF hospitalizations to 21.8% compared to 26.5% for enalapril treated patients. The absolute risk reductions were 4.7% for the composite of the CV death or HF hospitalization, 3.1% for CV death alone, and 2.8% for first HF hospitalization alone. The relative risk reduction was 20% versus enalapril. This effect was observed early and was sustained throughout the duration of the study. The risk reduction was consistently observed across subgroups including gender, age, race, geography, NYHA class (II/III), EF, renal function, history of diabetes or hypertension, prior HF therapy, and atrial fibrillation. Sacubitril/valsartan improved survival with a significant reduction in all-cause mortality of 2.8% (sacubitril/valsartan, 17%, enalapril, 19.8%). The relative risk reduction was 16% compared with enalapril. PARADIGM-HF trial was stopped early at the third interim analysis because the pre-specified stopping boundary for an overwhelming benefit of sacubitril/valsartan had been crossed. (Hubers 2016, McMurray 2014 /N Engl J Med, McMurray 2014 /Eur J Heart Fail, McMurray 2013).

The recommended starting dose of sacubitril/valsartan is one tablet of 49 mg/51 mg BID. The dose should be doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg BID, as tolerated by the patient. According to current recommendations found in the Summary of Product Characteristics (SPC) of sacubitril/valsartan, if patients experience tolerability issues (systolic blood pressure [BP[≤95 mmHg, symptomatic hypotension, hyperkalemia, renal dysfunction), adjustment of concomitant medications or temporary down–titration or discontinuation of sacubitril/valsartan is recommended. No dose adjustment is required in patients with mild renal impairment (estimated GFR [eGFR] 60-90 ml/min/1.73 m^2) while a starting dose of 24 mg/26 mg twice daily is recommended in patients with moderate renal impairment (eGFR 30-60 ml/min/1.73 m^2).

According to the information given in the EPAR – product information (annex 1) on the pharmacokinetics of sacubitril/valsartan, following oral administration, sacubitril/valsartan dissociates into valsartan and the prodrug sacubitril. Sacubitril is further metabolized to the active metabolite LBQ657 by carboxylesterases 1b and 1c. Sacubitril and LBQ657 reach peak plasma concentrations in 1 hour and 2 hours, respectively. They are highly bound to plasma proteins (94-97%). LBQ657 is not further metabolized to a significant extent. Approximately 50-70% of sacubitril (primarily as LBQ657) is excreted in urine and 30-50% in feces. Sacubitril, LBQ657 and valsartan are eliminated from plasma with a mean elimination half-life of approximately 1.4 hours, 11.5 hours, and 9.9 hours, respectively. The pharmacokinetics of sacubitril, LBQ657 and valsartan are approximately linear over

a sacubitril/valsartan dose range of 24 mg sacubitril/26 mg valsartan to 97 mg sacubitril/103 mg valsartan. The valsartan contained within sacubitril/valsartan is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in sacubitril/valsartan are equivalent to 40 mg, 80 mg and 160 mg of valsartan, respectively. (Gu 2010, Hubers 2016).

2.4 ^{11}C-acetate

^{11}C-acetate is mainly used for quantification of oxidative metabolism and perfusion. Acetate is quickly metabolized into acetyl-CoA in living tissues. Acetyl-CoA can then either enter into the Krebs cycle (tricarboxylic acid or TCA cycle) which is the main route in the myocardium, or it can enter into structural lipids, mainly in tumours. (Grassi 2012).

After intravenous (iv.) injection of ^{11}C-acetate, the build-up phase of radioactivity in the tissue is related (but not linearly) to tissue perfusion. Washout of the radiolabel represents the formation of ^{11}C-CO_2 in tissue, and is therefore related to oxygen consumption (Buck 1991; Klein 2001). Uptake at later time points may represent the rate of fatty acid synthesis (Lewis 2014).

Clearance of ^{11}C-acetate from the myocardium has been found to be bi-exponential (Brown 1988, Brown 1989, Armbrecht 1989). The k_1 from bi-exponential and k_{mono} from mono-exponential clearance estimation are correlated to myocardial oxygen consumption (Buxton 1989, Armbrecht 1989, Sun 1998, Ukkonen 2001, Wong 2013). Parametric k_{mono} images can be computed and presented as polar maps (Kotzerke 1990, Miller 1990).

Several compartmental models have been presented to estimate myocardial oxygen consumption, as reviewed by Klein et al. in 2001. One-tissue compartment model analysis of ^{11}C-acetate data allows also quantification of myocardial perfusion at rest as well as under stress conditions (van den Hoff 2001, Sciacca 2001, Sörensen 2010). This model is a simplification of previous five-compartment model (van den Hoff 1996), and performed best in comparison to three other models (Timmer 2010). It was found to provide myocardial blood flow values in fairly good agreement with actual perfusion values in both healthy individuals and patients with hypertrophic cardiomyopathy over physiological flow ranges under baseline conditions (Timmer 2010), and a reliable index (k_2) of oxygen consumption (Wong 2013). Arterial blood curve is extracted from left ventricular region, and corrected for metabolism using population-based function. The most common method of analyzing myocardial oxygen consumption is based on mono-exponential fitting of clearance rate (k_{mono}) (Armbrecht 1989).

2.5 Rationale of the study

Even though proven effective in terms of clinical outcomes, mechanistic data about the effects of the novel ARNI sacubitril/valsartan are needed in patients with HF and reduced EF. The clinical benefits of sacubitril/valsartan (reduced hospitalizations and improvement of symptoms) can be seen within 30 days after the onset of

therapy, but the underlying functional mechanisms are not known (Hubers 2016, McMurray 2014 /N Engl J Med).

Mechanical efficiency of the heart is defined as the ratio of useful energy produced (i.e. stroke work) to the amount of oxygen consumed. Excessive oxygen consumption in relation to mechanical work, i.e. reduced efficiency of forward work, is a typical feature of the failing heart. (Knaapen 2008). Previous studies have shown that cardiac efficiency can be improved by therapies that improve symptoms and clinical outcomes in HF, including cardiac resynchronization therapy, inhibition of beta-adrenergic system and inhibition of the RAAS (Knaapen 2007). ACEIs reduce mean aortic pressure and systemic vascular resistance (SVR) (Burnier 2001). Because of the related reduction in the LV load, there is an immediate increase in stroke volume and stroke work while myocardial oxygen consumption is lowered, thereby augmenting mechanical efficiency. Decreased degradation of NPs with sacubitril/valsartan encounters natriuretic resistance in HF resulting in improved endothelial function, vasodilatation and natriuresis (Hubers 2016). However, it is not known whether these beneficial hemodynamic effects result in improved efficiency of the LV work.

Cardiac oxidative metabolism can be measured non-invasively using ^{11}C-acetate PET. Changes in cardiac efficiency can be seen faster (days-to-weeks) than structural changes in LV volume (months-to-years) (Knaapen 2007, Tuunanen 2008). Our hypothesis is that short-term therapy with sacubitril/valsartan added on standard HF therapy improves cardiac efficiency in patients with systolic HF.

2.6 Risk assessment

Based on the information presented in the SPC of valsartan, in controlled clinical studies with valsartan in patients with hypertension, the overall incidence of adverse drug reactions (ADRs) was comparable with placebo and was consistent with the pharmacology of valsartan. The safety profile seen in controlled clinical studies in patients with post-myocardial infarction and/or HF varied somewhat from the overall safety profile seen in hypertensive patients. This was speculated to be related to the patients' underlying disease. Renal failure and renal impairment are described as a common (≥ 1/100 to < 1/10) ADRs with valsartan. (Cohn 2001).

The most commonly reported adverse reactions during sacubitril/valsartan treatment are hypotension, hyperkalemia and renal impairment. Angioedema, but not airway compromise, has also been reported in patients treated with sacubitril/valsartan. The safety of sacubitril/valsartan in patients with chronic HF was evaluated in the study PARADIGM-HF. Hyperkalemia and serum potassium concentrations >5.4 mmol/l were reported in 11.6% and 19.7% of sacubitril/valsartan-treated patients and in 14.0% and 21.1% of enalapril-treated patients, respectively, whereas hypotension and clinically relevant low systolic BP (<90 mmHg and decrease from baseline of >20 mmHg) were reported in 17.6% and 4.76% of sacubitril/valsartan-treated patients compared with 11.9% and 2.67% of enalapril-treated patients, respectively. Discontinuation of therapy due to an adverse reaction in the double-blind period of the study occurred in 450 sacubitril/valsartan-treated patients (10.7%) and 516 enalapril-treated patients (12.2%). Based on the

information presented in the SPC of sacubitril/valsartan, other very common (≥1/10) and common (≥1/100 to <1/10) adverse reactions during sacubitril/valsartan treatment include e.g. anemia, hypokalemia, hypoglycemia, headache, cough, diarrhea, nausea, gastritis, fatigue and asthenia. (Hubers 2016, McMurray 2014 /N Engl J Med).

Marked hypotension is the most likely symptom of overdose with both valsartan and sacubitril/valsartan, due to their BP lowering effects (Hubers 2016, McMurray 2014 /N Engl J Med, Cohn 2001). Marked hypotension can lead to depressed level of consciousness, circulatory collapse and/or shock. In cases of marked hypotension, symptomatic treatment should be provided.

Regarding other concomitant medications that may be used by the study subjects, the following possible interactions have to be considered: according to the SPC, concomitant use of valsartan is not recommended with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels. Caution is required when valsartan is used concomitantly with non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors and acetylsalicylic acid >3 g/day.

In vitro data indicate that sacubitril inhibits organic anion-transporting polypeptide OATP1B1 and OATP1B3 transporters. Sacubitril/valsartan may therefore increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins and caution should be exercised when co-administering these medications. (Hubers 2016). Other drugs that may have possible interactions with sacubitril/valsartan include NSAIDs, potassium containing or elevating drugs, lithium, furosemide and nitrates.

This study involves two PET-scans with ^{11}C-acetate. These scans cause exposure to ionizing radiation, which is harmful to living organisms. The total radiation dose from two up to 500 MBq ^{11}C-acetate PET tracer injections and low-dose CT scans for attenuation correction will be 7.5 mSv.

The current study with its design, including specific inclusion and exclusion criteria and study schedule and procedures, is aimed to minimize the risks (e.g. previously described possible adverse reactions and possible drug interactions) on subjects while participating in this study. Subject safety will be monitored throughout the study and the investigators will have the option to down-titrate the dose of the study medication or discontinue the subject's participation in the trial altogether, if they think that continuation would be detrimental to the subject's well-being. Subjects will be advised to contact the study site if they have new/worsening symptoms they feel may be due to the study treatment and/or instability of their HF therapy. During the scheduled visits, subject safety will be monitored with BP measurements (at site visits) and laboratory tests (including serum potassium and creatinine). Unscheduled visits may be performed at any time, if required, based on the investigator's clinical judgement.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary objective and endpoint

The primary objective of the study is to evaluate the effects of 6 weeks of stable sacubitril/valsartan therapy, as compared with valsartan therapy, on the efficiency of cardiac work in patients with NYHA II-III HF and reduced systolic function using ^{11}C-acetate and echocardiography.

In order to do this, the difference in cardiac efficiency will be evaluated by comparing the results obtained after 6 weeks of stable treatment to the results from the baseline visit.

3.2 Exploratory objectives and endpoints

The exploratory objective of the study is to evaluate the effects of 6 weeks of stable sacubitril/valsartan therapy, as compared with valsartan therapy, on myocardial oxygen consumption and cardiac and systemic hemodynamics.

In order to do this, the difference in the following cardiac and systemic hemodynamic parameters will be evaluated as exploratory endpoints: EF, NT-proBNP, systemic BP, SVR, coronary vascular resistance and cardiac oxygen consumption.

4 STUDY DESIGN

4.1 Type and design of the study

This is a phase IV, prospective, randomized, double-blind, double-dummy, parallel-group study performed at a single center that is formed by [redacted]. The subjects enrolled into this study will be patients with chronic HF who fulfill all of the inclusion criteria and none of the exclusion criteria. No more than 50% of the study subjects are allowed to have diabetes. The study will have two treatment arms, the sacubitril/valsartan treatment arm and the valsartan treatment arm, and the subjects will be randomized into these arms in a 1:1 ratio. The study will be performed in a double-blind manner in regards to the treatment the subjects receive during the treatment period. As the sacubitril/valsartan and valsartan tablets are not similar in appearance, the study will be performed in a double-dummy manner in order to maintain blinding, i.e. the subjects will take 2 tablets BID, either active valsartan + placebo for sacubitril/valsartan *or* active sacubitril/valsartan + placebo for valsartan. Regardless of the treatment arm a subject is in, the study drug will be up-titrated to the highest tolerated dose level during the scheduled study visits. The different strengths of the two study drugs are not identical in appearance so the possible dose modification(s) during the treatment period cannot be performed in a blinded manner. Subjects will start on valsartan 80 mg BID or sacubitril/valsartan 100 mg BID dose and there will be only one scheduled up-titration visit after the randomization. Exception for this are the subjects that are on valsartan 160 mg BID dose during the run-in phase.

These subjects will be randomized directly to valsartan 160 mg BID or sacubitril/valsartan 100 mg BID. Subjects that are randomized to valsartan arm will have similar visit after which they will continue on the same dose. For subjects that were randomized from valsartan 160 mg BID to sacubitril/valsartan 100 mg BID the dose will be up-titrated to 200 mg BID if clinically possible. If clinically indicated, dose alterations will be allowed up to week 4 after randomization. In order to be eligible for the final study assessments on visit 3 (i.e. the ^{11}C-acetate PET-scan and echocardiography), the subjects have to be on a stable dose for at least 6 weeks on one of the following treatment options: valsartan 80 mg BID or 160 mg BID or sacubitril/valsartan 100 mg BID or 200 mg BID. Study drug dispensing during the treatment period will be performed by an unblinded member of the study team and the study drugs will be self-administered by the subjects at home. To achieve similar groups, the number of subjects with renal insufficiency (GFR 45-60 or >60 mL/min/1.73m^2) and/or diabetes mellitus (on insulin or oral glucose-lowering therapy) will be balanced in the treatment arms by stratified randomisation. The baseline HF therapy (the number of subjects that are on valsartan 160 mg BID at the time of randomization) will be also balanced between the treatment arms.

4.2 Randomization and blinding

The subjects will be randomized in a 1:1 ratio to one of the two treatment arms, either the sacubitril/valsartan treatment arm or the valsartan treatment arm. Stratified randomization will be used to achieve similar groups in terms of patients with renal insufficiency (GFR 45-60 or >60 mL/min/1.73m^2) and/or diabetes mellitus (on insulin or oral glucose-lowering therapy, no more than 50 % of patients in the study are allowed to be diabetic). The baseline HF therapy (the number of subjects that are on valsartan 160 mg BID at the time of randomization) will also be taken into account during randomization.

Study drug packages will be provided from Novartis with removable labels stating the treatment. Treatment allocation will be done by an un-blinded member of the study team who will remove the labels stating the treatment before distributing the study drug packages to the subjects.

The randomization will be generated by an independent statistician at [redacted] using SAS®.

Sealed envelopes containing the individual treatment codes (randomization number and the corresponding treatment) will be stored adjacent to the investigational medicinal products (IMPs) until the end of the trial. In case of an emergency requiring immediate knowledge of the treatment administered, the code of an individual subject may be opened. The reasons for opening the code have to be documented and the subject has to be discontinued from the study. The study monitor and the sponsor should be immediately informed about breaking of the treatment code.

This study will be conducted in a double-blinded fashion regarding the treatment (i.e. sacubitril/valsartan or valsartan). As the sacubitril/valsartan and valsartan tablets differ in appearance, the study has to be performed in a double-dummy manner with the subjects taking one active tablet and one placebo tablet BID. The different

strengths of the two study drugs are not identical in appearance so the possible dose modification(s) during the treatment period cannot be performed in a blinded manner. However, the up-titration step will be aligned in both treatment arms – the subjects will start on valsartan (80 mg BID or 160 mg BID) or sacubitril/valsartan (100 mg BID) and there will be only one scheduled up-titration visit after the randomization. The subjects that start from valsartan 160 mg BID will have similar scheduled visit but will stay on the same dose.

Valsartan used in the screening/run-in period will be taken from local commercial stock and will be labelled by Tamro. Study drugs for the treatment period of this study are manufactured by Novartis, in accordance with Good Manufacturing Practice (GMP) guidelines. Supplies for the study will be packed and labelled in compliance with GMP regulations and then released at Novartis. The different strengths of the study drugs and the corresponding placebo tablets will be packed in separate study drug packages and an appropriate number of these study drug packages will be provided to the study site. The study drug packages containing the different strengths of the specific treatment (i.e. sacubitril/valsartan or valsartan) and placebo will be labelled in a way that does not reveal the treatment arm; the removable labels stating the treatment will be removed before dispensing the packages to the subjects. The possible up-titration of the study drug dose will be decided by the investigator based on the subject's clinical status and safety assessments. A schematic figure on the treatment arms and the possible doses is given in Section 6.1 (Figure 2 and 3).

At screening visit 1, subjects who have signed the Informed Consent form (ICF) will be given screening numbers beginning from 1-1001. Once enrollment has been confirmed, subjects will receive randomization numbers from the stratum-specific list and will be allocated to the treatment assigned to each randomization number as indicated by the randomization lists. If an enrolled subject discontinues the study, the investigator (after consulting with the sponsor) will decide on a case-by-case basis about including an additional subject into the study.

4.3 General study outline

The total duration of the study is planned to be about 14 weeks for each subject, but it may be longer if required for scheduling purposes (e.g. availability of PET slots, subject's schedule). During the study, the subjects will have 5-6 study visits, depending on the need for safety visits (visit 2; see Table 3). Two of these visits, screening visit 2 and visit 2, may performed as a remote visit (i.e. telephone contact), if deemed sufficient by the investigator. In addition, unscheduled visits may occur at any time, if considered necessary for subject safety. The study includes a screening/run-in period (up to 6 weeks) and a treatment period (approximately 8 weeks). Both the screening/run-in and the treatment period may be longer, if necessary (see Section 7.1 for further details).

The subjects who sign the ICF will enter the screening/run-in period of the study. All study-related procedures will be performed only after the ICF has been signed. During the first study visit, the investigator will consider the subject's eligibility based on his/her medical history and current clinical status (including e.g. BP). If based on

these considerations, the subject is found to be likely to fulfill all of the inclusion criteria and none of the exclusion criteria, the subject will be switched to valsartan treatment and it will replace his/her previously used ACEI or ARB treatment during the screening/run-in period. The starting dose of valsartan will be 80 mg BID or if the dose of previous RAAS blockage medication has been higher, the valsartan dose will be 160 mg BID to ensure that the subjects' medication level is not down-titrated in the beginning of the screening/run-in period. Approximately one week after the screening visit 1, screening visit 2 will be scheduled in order to evaluate the safety and efficacy of the ongoing valsartan treatment. If deemed sufficient by the investigator, screening visit 2 can be performed remotely. If so, safety blood sampling, eligibility criteria review, adverse events and concomitant medication must be assessed. Only subjects who tolerate 80 mg BID or 160 mg BID of valsartan and can maintain a stable dose for at least 4 weeks will be eligible to enter into the treatment period.

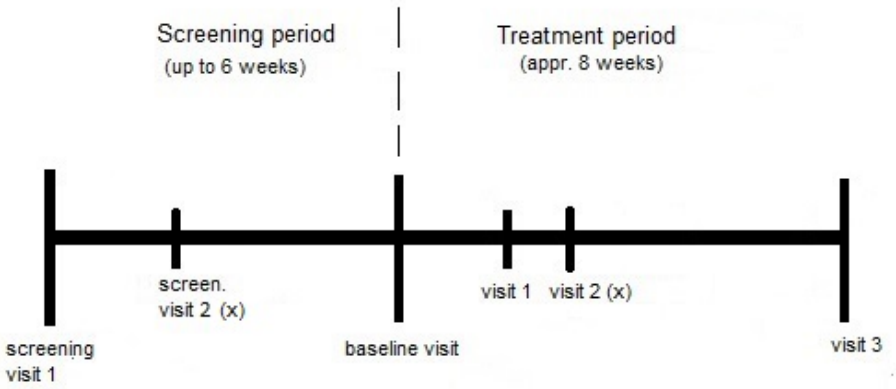
After the screening evaluations and confirmation of eligibility, the subjects will be allocated randomization numbers and randomized to receive the treatment assigned to each number in a blinded manner. Study drugs will be dispensed by an unblinded member of the study team member during the treatment period while the study personnel directly involved in the clinical assessments will remain blinded throughout the study. The starting dose for each subject in the sacubitril/valsartan arm will be 100 mg BID and in the valsartan arm 80 mg BID or 160 mg BID (see Figures 2 and 3). The study subjects will return to the study center 2-3 times during the treatment period at the following time points: approximately 2 weeks (visit 1), 3 weeks (visit 2) and 8 weeks (visit 3) after the start of the treatment period.

During visit 1, treatment tolerability will be evaluated and possible dose up-titration will be considered. Every subject should be attempted to be up-titrated to the next dose level (sacubitril/valsartan 200 mg or valsartan 160 mg, if the latter needed), if clinically possible. If up-titration is not possible, the starting dose should be maintained. The intent of visit 2 (week 3) is to confirm subject safety on the dose level that is likely to be maintained for the rest of the study. If deemed sufficient by the investigator, visit 2 can be performed remotely. If so, safety blood sampling, adverse events and concomitant medication must be assessed.

After visit 2, if clinically indicated, the dose of the study treatment may be modified (up- or down-titrated) up to week 4. If study drug dose is modified within this time, an unscheduled visit should be performed to assess subject safety on the new dose level. During the treatment period, the subjects will self-administer two tablets from two study drug packages BID (one tablet from the study drug package containing the active treatment and one tablet from the study drug package containing the placebo). The last study visit will include the final efficacy assessments, i.e. the ^{11}C-acetate PET-scan and the echocardiography.

The general study design is presented in Figure 1 and the study outline is presented in Table 3. The methods and timing of assessments and recording of efficacy, safety, tolerability and other measures are described in detail in Section 8.

Figure 1. General study design



Screening visit 2 and visit 2 are marked with *(x)* as they may be performed remotely, if deemed sufficient by the investigator. In addition, visit 2 may be omitted altogether, if no dose modification was made on the previous visit (visit 1).

Table 3. General study outline

Study event	Screening visit 1	Screening visit 2 (R)	Baseline	Visit 1	Visit 2[1] (R)	Visit 3
	-5 weeks	- 4 weeks	day 1	day 14	day 21	week 8[2]
Informed consent	X					
Medical and surgical history	X					
Demographics	X					
Physical examination[3]	X	X*	X	X	X*	X
Blood pressure and heart rate[4]	X	X*	X	X	X*	X
Safety blood samples[5]	X	X	X	X	X	X
Blood biomarker samples			X			X
Decision on up- or down-titration				X	X*	
Eligibility criteria review	X	X	X			
Urine pregnancy test[6]			X			X
^{11}C-acetate PET-scan			X			X
Echocardio-graphy			X			X
Randomization			X			
Valsartan dispensing[7]	X	X*				
Study drug dispensing[7]			X	X	X*	
Instruction on drug intake[7, 8]	X	X*	X	X	X*	
Return of drug supplies[9]		X*	X	X	X*	X
Compliance check[9]		X*	X	X	X*	X
Adverse events	X					
Concomitant medications	X					

R – If deemed sufficient by the investigator, screening visit 2 and visit 2 can be performed remotely (i.e. by telephone). If so, safety blood sampling, (eligibility criteria for screening visit 2 only), adverse events and concomitant medication must be assessed. If the visit is performed as a remote visit, assessments marked with "*" do not need to be performed.
[1] Visit 2 is a safety visit to be performed only for subjects whose dose was modified on visit 1 and/or if clinically indicated based on the investigator's decision. For subjects whose dose is not up-titrated on visit 1, visit 2 may be omitted.
[2] Visit 3 will be performed after the study treatment has been on a stable dose for a minimum of 6 weeks. It may be performed before or after 8 weeks, based on when the last dose modification was performed.
[3] Physical examination is part of clinical assessment and will take place on every site visit.
[4] Blood pressure and heart rate will be measured in a seated position, after at least 5 min of rest.
[5] Safety blood samples may be collected 1-2 business day(s) before the scheduled visit (with the exception of screening visit 1).
[6] For female subjects of childbearing potential.
[7] Study drugs will be dispensed by an unblinded member of the study team during the double-blinded treatment period. Valsartan may be dispensed by any member of the study team during the screening/run-in period.
[8] Instructions on drug intake have to be given at the start of each period and thereafter only if clinically indicated or significant non-compliance is detected.
[9] These study events include both the valsartan treatment during the screening/run-in period and the double-blinded study drug treatment during the treatment period.

5 SUBJECTS

5.1 Source population

The subjects participating in this study will be patients with chronic HF, reduced EF and NYHA class II-III symptoms who fulfill all of the inclusion criteria and none of the exclusion criteria. The results of the screening evaluations will determine whether a subject can be included in the study or not.

5.2 Number of subjects

The planned number of enrolled study subjects is 60 (30 subjects/treatment arm). The aim is that at least 27 subjects/treatment arm finish the study according to the protocol. If discontinuations occur, the need of recruiting additional subjects to reach the targeted total number of subjects will be considered and carried out as appropriate. Thus, in case of discontinuations during the study, the number of enrolled study subjects may be larger than 60.

For justification of sample size, see Section 9.1.

5.3 Inclusion criteria

Subjects have to fulfill all of the following inclusion criteria to be eligible for inclusion in this study.

1. Voluntary, valid written informed consent (IC) obtained before any study-related assessment is performed.
2. Sufficient command of the Finnish or Swedish language to be able to fully understand the ICF and other study information and to be able to communicate with the study personnel.
3. Male and female subjects ≥40 and ≤80 years of age.
4. Documented chronic HF with left ventricle EF 25-35% and NYHA class II-III symptoms.
5. Systolic BP 110-160 mmHg at the time of randomization.
6. Optimal standard HF therapy according to ESC guidelines, including at a minimum beta-blockers in all subjects, at a stable dose for at least 4 weeks before the first screening visit.
7. Valsartan treatment tolerated at a dose of 80 mg or 160 mg BID for at least 4 weeks during the screening/run-in period.

5.4 Exclusion criteria

Subjects fulfilling any of the following exclusion criteria are not eligible for inclusion in this study.

1. Predicted poor compliance or inability to communicate well with the investigator or the study center personnel.
2. Current acute or subacute decompensated HF.
3. Presence of acute coronary syndrome, stroke, transient ischemic attack or other major cardiovascular event or cardiovascular procedure within 3 months before screening.
4. Coronary or carotid artery disease likely to require surgical or percutaneous intervention within the 6 months after randomization.
5. Evidence of clinically significant renal, hepatic, hematological, gastrointestinal, pulmonary, metabolic-endocrine, neurological, urogenital or psychiatric disease that may constitute a health risk for the subject and/or would interfere with the evaluation of the results, as judged by the investigator.
6. Symptomatic hypotension that persists even after modification of concomitant medication(s), at any time during the screening/run-in period.
7. Estimated glomerular filtration rate (eGFR) < 45 ml/min at any time during the screening/run-in period that persists even after modification of concomitant medication(s).
8. Serum potassium >5.2 mmol/l at any time during the screening/run-in period that persists even after modification of concomitant medication(s).
9. Serum creatinine > 1.5 x ULN (upper limit of normal) at any time during the screening/run-in period that persists even after modification of concomitant medication(s).

10. Contraindication to neprilysin inhibitor or ARB (such as previous angioedema or known intolerance).
11. Susceptibility to severe allergic reactions or known hypersensitivity to the active substances or to any of the excipients.
12. Intake of any medication that could affect the outcome of the study, interfere with the evaluation of the results or constitute a health risk for the study subject, as judged by the investigator.
13. Positive serology to human immunodeficiency virus antibodies (HIVAgAb), hepatitis C virus antibodies (HCVAb) or hepatitis B surface antigen (HBsAg) in medical history.
14. Unwillingness to use adequate methods of contraception while participating in the study and for 3 months after the last administration of the PET tracer.
15. Participation in another clinical drug study within 3 months prior to the first study treatment administration of this study.
16. Prior participation in an investigational PET study or other medical or occupational exposure to significant doses of ionizing radiation, as judged by the investigator.

5.5 Recruitment

The subjects will be recruited from the patient population of the hospital district of Southwest Finland. A description of the possible means of subject recruitment is included in the submission to the Ethics Committee (EC). The recruitment of subjects will start after approvals have been received from the EC and Competent Authority (CA).

The investigator or an appropriate designee will look over the medical records of the patients treated in the hospital district of Southwest Finland. If needed, colleagues of the investigator may be informed about the study to aid in recruitment. Possibly suitable subjects will be contacted and the person responsible for subject recruitment will first shortly brief the potential subjects about the study in layman's language. This first study-related contact may be performed also in person, if the subject candidate is on site. The main inclusion and exclusion criteria will be checked during telephone contact or face-to-face conversation. If an inclusion criterion is not fulfilled, or an exclusion criterion is fulfilled, this is immediately told to the subject, and the interview is terminated. If, according to this preliminary evaluation, the subject candidate might be eligible for the study, the procedures for providing the written subject information are discussed. The subject information leaflet and the ICF are handed over to the subject or delivered to him by post, e-mail or another method. The next steps in the recruitment process will be agreed upon, as convenient to the subject and as defined in the protocol. Upon the subject candidate's wish, a screening visit may be booked or performed on-site after signing the ICF (all study-related assessments will be performed after signing the ICF).

The subjects will be told what personal information of them will be collected and how it will be stored and processed. The collection of personal information is described in a Description of the Personal Data Register, which is kept in the Investigator's Study File (ISF) and is made available to the subjects, if they wish.

5.6 Study subject screening log and identification log

The investigator will keep a subject identification list in the ISF. The list includes information to link all study-related records to a subject, i.e. randomization list, case report forms (CRFs) and source data. Furthermore, a subject screening log of all subjects screened for the study will be maintained. The identity of the subject (screening number, the subject's first name, last name and personal identity number), date of IC, date of entry or date of exclusion and the reason for exclusion, if applicable, for those recruited for screening but not fulfilling the criteria and therefore excluded, should be recorded on the list.

5.7 Instructions concerning lifestyle and concomitant treatments

The subjects are instructed to keep their usual dietary and exercise habits during their participation in the study. Blood donation is not allowed during the study. Female subjects of childbearing potential and male subjects with female partners of childbearing potential should be instructed to use adequate methods of contraception while participating in the study and for 3 months after the last administration of the PET tracer. Urine pregnancy tests will be performed for females of childbearing potential prior to each PET scan. Use of alcohol and caffeine-containing beverages is forbidden for 12 h before each PET-scan. In addition, a study subject shall not participate concurrently or have participated in any other clinical drug trial within 3 months prior to entry into this study. Instructions regarding concomitant treatments can be found in Section 6.5.

5.8 Withdrawal of subjects

Study subjects are free to withdraw from the study at any time without providing a reason. However, the investigator should try to find out the reason and document it on the corresponding CRF page. A subject may also be withdrawn from the study if his/her adherence to the study protocol is not acceptable. A study subject needs to discontinue the study if the investigator considers that continuation in the study would be detrimental to the subjects well-being. The following situations should result in the withdrawal of the subject, unless the investigator considers it safe for the subject to continue in the study, possibly after dose modifications of the study drug or other concomitant medication:

- persistent symptomatic hypotension after randomization;
- serum potassium > 5.2 mmol/l after randomization;
- serum creatinine > 1.5 x ULN after randomization.

If the subject continues in the study, the investigator has to document his/her decision in the source documents and verify continuous subject safety with e.g. repeat BP surveillance and/or laboratory safety measurements during unscheduled visit(s).

Irrespective of the reason for discontinuation, discontinued study subjects should be invited for an unscheduled visit as soon as possible in order to perform final safety

assessments (incl. BP, safety laboratory tests and possibly other tests judged necessary by the investigator). The CRFs should be as complete as possible.

If discontinuations occur, the need of recruiting additional subjects to reach the targeted total number of subjects will be considered and carried out as appropriate. Discontinued study subjects are not allowed to re-enter the study.

5.9 Information to be collected on screening failures

From subjects screened but not included in the study, the following data will be collected on CRFs: date of IC, demography (year of birth, sex and race), the inclusion/exclusion criterion/criteria causing the exclusion and the date of the decision of exclusion.

6 TREATMENTS

6.1 Investigational treatment sacubitril/valsartan

The IMP, sacubitril/valsartan, will be provided in appropriately labelled study drug packages of the different strengths of the active drug. Also, corresponding placebo tablets that are similar in appearance to the active sacubitril/valsartan will be provided. The following strengths of sacubitril/valsartan will be available:

- sacubitril/valsartan 100 mg: containing 49 mg sacubitril/51 mg valsartan,
- sacubitril/valsartan 200 mg: containing 97 mg sacubitril/103 mg valsartan.

The IMP is manufactured by Novartis in accordance with GMP guidelines. The labelling will be also done in compliance with GMP regulations after which the study drug will be released at Novartis. The sacubitril/valsartan will be stored in the Heart Center in locked cabinets according to the instructions provided in the SPC. The subjects will receive their study treatment according to the randomization list which contains randomization numbers and allocated treatments. The study drugs will be dispensed by an unblinded member of the study team and the subjects will take the study drugs and corresponding matching placebo tablets at home BID. After the randomization, 50% of the subjects will start in the sacubitril/valsartan treatment arm on a starting dose of 100 mg BID (see Figure 2). There is one visit scheduled for possible up-titration of the dose (visit 1) and during this visit every subject should be attempted to be up-titrated to the next dose level (sacubitril/valsartan 200 mg or valsartan 160 mg), if clinically possible and if the latter needed. If up-titration is not clinically possible, the starting dose should be maintained. During the treatment period, subjects will receive new study drug packages (active drug and placebo) from the unblinded drug dispenser, as applicable.

The study subjects and all investigators and other study personnel participating in the assessments will be kept blinded to the treatments but not the dose level.

A schematic figure about the possible treatments and doses is shown in Figures 2 and 3.

Figure 2. Study treatment during the double-blind treatment period with sacubitril/valsartan.

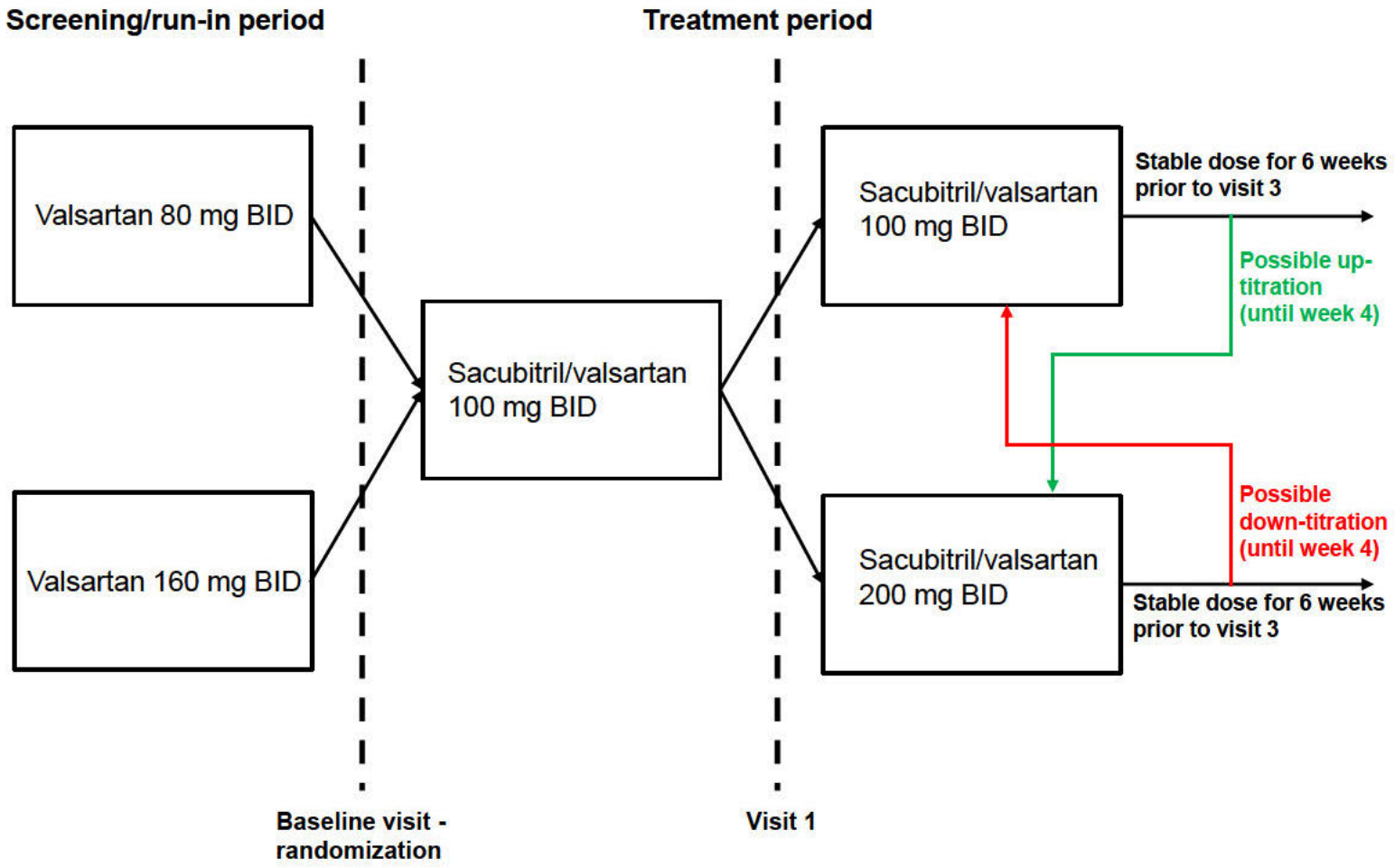
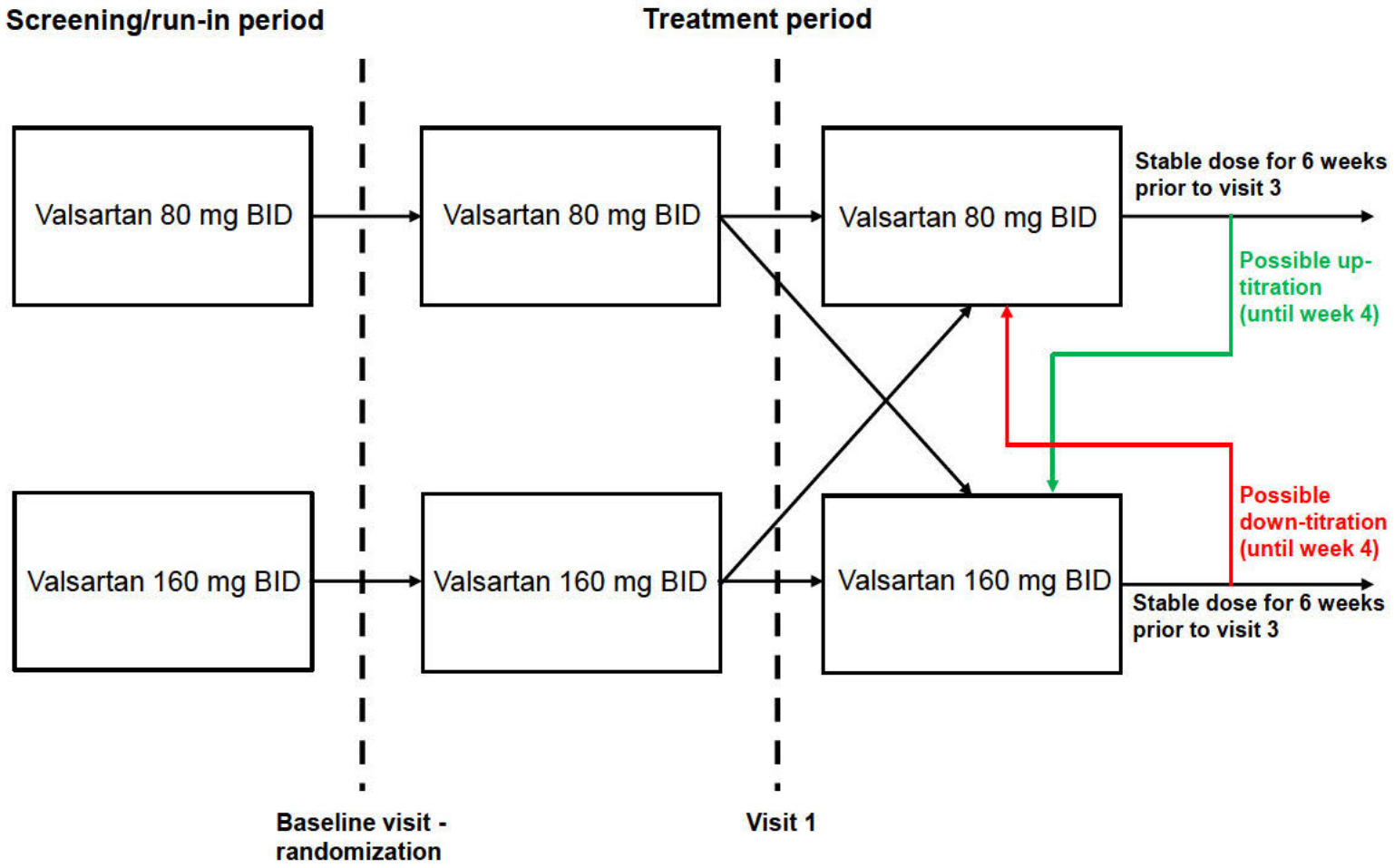


Figure 3. Study treatment during the double-blind treatment period with valsartan.



6.2 Control treatment

Valsartan will be used as control treatment during the study. Its use aims to standardize background therapy for efficacy and hemodynamic effects in order to assess the incremental effects of combined angiotensin receptor (ATR) inhibition and neprilysin inhibition therapy as compared to ATR inhibition alone. Valsartan will replace previously used ACEI or ARB in all subjects during the screening/run-in period on a dose of 80 mg BID or 160 mg BID, if the dose of previous RAAS blockade was higher than 80 mg BID or equivalent. In order to be eligible for the study, a minimum dose of valsartan 80 mg BID has to be tolerated by the subject.

Valsartan will be provided in appropriately labelled study drug packages of the different strengths of the active drug. Also, corresponding placebo tablets that are similar in appearance to the active valsartan will be provided. The following strengths of valsartan will be available:

- valsartan 80 mg (used in both the screening/run-in period – not blinded – and also after randomization in a blinded manner),
- valsartan 160 mg (used in both the screening/run-in period – not blinded – and also after randomization in a blinded manner).

For the screening/run-in period, valsartan will be taken from local commercial stock and subsequently labelled as a research drug by Tamro. During the screening/run-in period, valsartan can be dispensed by any member of the study team. For the treatment period, valsartan is manufactured by Novartis in accordance with GMP guidelines. The labelling will be also done in compliance with GMP regulations after which the study drug will be released at Novartis. Valsartan will be stored in the Heart Center in locked cabinets according to instructions provided in the SPC. The subjects will receive their study treatment according to the randomization list which contains randomization numbers and allocated treatments. During the treatment period, the study drugs will be dispensed by an unblinded member of the study team and the subjects will take the study drugs and corresponding matching placebo tablets at home BID. After the randomization, 50% of the subjects will continue in the valsartan treatment arm, on a starting dose of 80 mg BID or 160 mg BID if they were on this dose during the screening/run-in (see Figure 3). There is one visit scheduled for possible up-titration of the dose (visit 1) and during this visit every subject should be attempted to be up-titrated to the next dose level (sacubitril/valsartan 200 mg or valsartan 160 mg, if the latter needed), if clinically possible. If up-titration is not clinically possible, the starting dose should be maintained. During the treatment period, subjects will receive new study drug packages (active drug and placebo) from the unblinded drug dispenser, as applicable.

6.3 PET-tracer ^{11}C-acetate

PET-tracer synthesis will be done according to the standard operating procedures (SOPs) of [redacted]. ^{11}C-acetate is synthesized by reaction of ^{11}C-carbon dioxide with methylmagnesium bromide in diethyl ether. Labelling reaction is stopped by addition of dilute acetic acid and reaction product is purified with solid

phase extraction, formulated for iv. injection and filtered through sterile filter. The radioligand preparation will undergo quality control tests before each intravenous bolus administration.

6.4 Handling of the study products

Study products will be kept in locked and temperature-monitored storage facilities at the Heart Center until dispensing to study subjects. Separate written instructions on the storage conditions are provided in the SPCs of valsartan and sacubitril/valsartan. The shelf-life and storage conditions will be available on the labels of the study drug packages. The study drugs, both sacubitril/valsartan and valsartan, will be tablets for oral administration provided in sealed study drug packages. Any member of the study team may dispense valsartan to the subjects during the screening/run-in period, but only an appointed unblinded member of the study team is allowed to dispense the study drugs (active drug and placebo) during the treatment period.

Manufacturing, packaging and labelling of ^{11}C-acetate will comply with GMP and standard practices at [redacted].

6.5 Prior and concomitant treatments

The subjects must be on a stable and optimal standard HF therapy according to ESC guidelines prior to participation in the study. The therapy must be at a stable dose for at least 4 weeks before the first screening visit and must include at a minimum beta-blocker and ACEI or ARB in all subjects. Valsartan will replace previously used ACEI or ARB on a dose of 80 mg BID or 160 mg BID if the dose of previous ACEI or ARB was higher than equivalent to 160 mg BID valsartan. The use of spironolactone is allowed, if at a stable dose for at least 4 weeks before the first screening visit. Dose reduction of loop diuretics is allowed during the study at all times to prevent hypotension. The HF therapy should otherwise remain unchanged throughout the whole study (i.e. until visit 3).

Concomitant medication(s) required for treatment of subjects' concurrent diseases are allowed during the study, with the exception of medication(s) that could affect the outcome of the study, interfere with the evaluation of the results or constitute a health risk for the study subject, as judged by the investigator. These include e.g. vasoactive supporting medication(s) that have known effects on cardiac efficiency.

All concomitant treatments administered during the study must be recorded on the CRF page for concomitant treatments. No other investigational treatment is allowed to be used during the study. A study subject must not participate concurrently or have participated in any other clinical drug study within 3 months prior to the first study treatment administration of this study.

6.5.1 Prohibited treatments during the study

Concomitant medication(s) that could affect the outcome of the study, interfere with the evaluation of the results or constitute a health risk for the study subject, as judged by

the investigator. These include e.g. vasoactive supporting medication(s) that have known effects on cardiac efficiency.

6.5.2 Permitted treatments during the study

Optimal standard HF therapy and other concomitant medication(s) needed for treatment of possible concurrent diseases are allowed.

6.6 Emergencies and treatment of adverse events

Emergencies will be treated according to the decision of the physician in charge or the investigator when available. The treatment of possible AEs will be primarily symptomatic.

Any relevant control or follow-up examinations may be initiated at any time by the investigator. In case of any clinically significant abnormalities, medical assistance is assured until complete resolution or stabilization.

6.7 Procedures for monitoring subject compliance

During the screening/run-in period, the subjects will take one tablet of valsartan twice a day at home. During the treatment period, the subjects will take one tablet of active drug and one placebo tablet twice a day at home. They will be instructed to take valsartan (during the run-in) and the study drugs (active and placebo) in the morning and in the evening. In case a subject forgets to take the tablet(s) in the morning or in the evening, he/she is instructed to take the next one at the next scheduled drug intake time. At each administration time during the treatment period, the subjects are instructed to take one tablet from each of the two study drug packages they were provided with at a previous site visit. Two study drug packages (one containing the active drug and one containing the placebo) will be dispensed to the subjects at the baseline visit and at visit 1 by an unblinded member of the study team. In case the dose of the study drug is down-titrated during the treatment period, new study drug packages may be dispensed after visit 1. The subjects will be asked to return the study drug packages at each site visit, with all of the unused tablets, both during the screening/run-in and treatment period. Study personnel will do a valsartan and study drug/placebo accountability check and record this when applicable (i.e. at baseline visit and visits 1 and 3; also at screening visit 2 and visit 2, if they are performed as site visits). Valsartan accountability check during the screening/run-in period may be performed by any member of the study team, whereas study drug/placebo accountability check during the treatment period has to be performed by the unblinded member of the study team.

Drug accountability records will be kept. The investigator or his/her delegate must maintain accurate written records demonstrating the date and amount of study drugs received at the site, to whom and by whom dispensed (drug dispensing list) and accounts of drugs accidentally or deliberately destroyed. Unused study drugs will be recorded and returned to the sponsor or disposed of, on the sponsor’s consent. Any

discrepancies between the returned and expected returned study drugs should be explained.

7 VISIT SCHEDULE

7.1 Screening/run-in period

The screening/run-in period can last up to 6 weeks, but is not intended to last over 4 weeks, before the first study drug administration in the double-blinded treatment period. In certain cases, if clinically indicated (e.g. tolerability issues) or necessary for other reasons (e.g. scheduling), the screening/run-in period may last longer than 6 weeks. Screening/run-in period extensions (over 6 weeks) must be justified by the investigator and the reasons documented. Screening/run-in safety assessments should be repeated, based on investigator's judgement and/or if necessary, so that the laboratory results and the latest BP values are no older than 6 weeks.

During the first screening visit, a potential study subject will receive both written and verbal information on the study and will have an opportunity to ask questions and sufficient time to make up his/her mind concerning participation in the study. A signed and dated written IC will be obtained. All study-related assessments will be performed after the ICF has been signed.

At the first screening visit, subjects who have signed the ICF will receive screening numbers starting from 1-1001, and after assessment of inclusion and exclusion criteria, enrolled subjects will receive randomization numbers from the stratum specific list. During the screening/run-in period, the subjects will be interviewed for their relevant medical and surgical history and their prior and current use of medications. Demographic data will be also collected. This information may also be obtained from the subject's medical records, if available. If medical charts are used, relevant medical history events and concomitant medications should be verified with the subject (in order to ensure the subject does not use any medication not in his/her medical records). BP will be measured and safety laboratory tests will be performed at the first screening visit. If the investigator considers the subject to be eligible for the study based on these initial investigations, the subject may continue in the screening/run-in period.

During the screening/run-in period, the subjects will receive valsartan treatment that will replace their previous ACEI or ARB HF therapy. Valsartan during the screening/run-in period may be dispensed by any member of the study team. The screening/run-in dose of valsartan (80 mg BID or 160 mg BID) will be decided by the investigator based on the subject's clinical status, prior HF therapy and concomitant medications. The subjects will have a scheduled safety and efficacy assessment visit during the screening/run-in period (screening visit 2 in the study schedule, Table 3). If deemed sufficient by the investigator, screening visit 2 can be performed remotely. If so, safety blood sampling, eligibility criteria review, adverse events and concomitant medication must be assessed.

Dose reduction of a loop diuretic is allowed during the screening/run-in to prevent hypotension. Unscheduled visits may be performed at any time during the screening/run-in period. Study visit should be performed as close proximity to the stated day in the study schedule (Table 3) as possible.

The subject has to tolerate at the minimum 80 mg BID valsartan at a stable dose for minimum of 4 weeks in order to be eligible for the treatment period. Before the PET-scan, a urine pregnancy test should be performed for female subjects of childbearing potential. During the baseline visit, PET-scan and echocardiography will be done and blood samples for biomarker assessment will be drawn. After all other study procedures are performed at the baseline visit and the subject is deemed eligible for the study, he/she will be randomized and start the double-blinded treatment period.

The results for the laboratory tests taken during the on-site screening visits do not need to be available before decision-making (i.e. starting valsartan treatment), but they have to be reviewed as soon as possible after they become available in order to ensure subject safety. All screening/run-in period laboratory results must be available and reviewed before randomization, except the results of the laboratory tests taken on the baseline visit, as randomization is performed on the same day as the baseline visit.

Adverse events and changes in concomitant medications will be recorded throughout the screening/run-in period.

A subject will be entered into the study at the time of randomization, after the baseline PET-scan and echocardiography have been performed, if all inclusion criteria and none of the exclusion criteria are met.

For a detailed description on the information to be recorded during the screening/run-in period, please refer to Section 8.1.

7.2 Treatment period

The treatment period will last for approximately 8 weeks for each subject (it may be longer if required for clinical and/or scheduling purposes). During this time, the subjects will receive either sacubitril/valsartan or they will continue in the valsartan treatment arm. The subjects will be randomized into one of these two treatment arms in a 1:1 ratio. Study drugs during the treatment period will be dispensed by an unblinded member of the study team. As the different treatments, valsartan and sacubitril/valsartan, and the different strengths of these treatments are not similar in appearance, the study will be performed in a double-dummy manner, i.e. the subjects will take two tablets BID throughout the treatment period. The following options are possible:

- valsartan + placebo for sacubitril/valsartan,
- sacubitril/valsartan + placebo for valsartan.

The starting dose in the sacubitril/valsartan treatment arm will be 100 mg BID and in the valsartan treatment arm it will be 80 mg BID or 160 mg BID. A schematic figure about the possible treatments and doses is shown in Figures 2 and 3, Section 6.1. During the treatment period, the dose of the study treatment will be up-titrated to the

highest tolerated dose, up to 160 mg BID (if needed) for valsartan and up to 200 mg BID for sacubitril/valsartan. There will be one visit scheduled for possible up-titration of the dose (visit 1) and during this visit every subject should be attempted to be up-titrated to the next dose level (sacubitril/valsartan 200 mg or valsartan 160 mg, if needed), if clinically possible. If up-titration is not clinically possible, the starting dose should be maintained. At the minimum, 80 mg BID of valsartan or 100 mg BID of sacubitril/valsartan has to be tolerated by the subject in order to finish the study – if these doses are not tolerated, the subject has to be withdrawn from the study. The decision to up-titrate the dose will be done by the investigator during the study visits based on the subject's clinical status and the safety assessments, incl. BP and safety laboratory tests. The laboratory results, if taken on the days of the on-site visits, do not need to be available before decision-making but they have to be reviewed as soon as possible to ensure subject safety. If the safety blood samples are collected 1-2 business day(s) before the scheduled visit, the laboratory results have to be available and reviewed before decision-making. Dose reduction of a loop diuretic is allowed during the up-titration to prevent hypotension.

The day the subject starts taking the double-blind study medication is Day 1 (i.e. day of randomization) and the subsequent visits will take place on Day 14 (visit 1) and Day 21 (visit 2). Study visits should be performed as close proximity to the stated day in the study schedule (Table 3) as possible. Ideally, the last dose modification is done on visit 1. Visit 2 is a safety visit to be performed only for subjects for whom the treatment dose was modified on visit 1 and/or if it is clinically indicated based on the investigator's decision. If deemed sufficient by the investigator, visit 2 can be performed remotely. If so, safety blood sampling, adverse events and concomitant medication must be assessed. For subjects whose dose is not up-titrated on visit 1, visit 2 may be omitted, based on investigator's decision that has to be documented. Unscheduled visits may be performed at any time during the treatment period. Dose modifications, including up- and possible down-titrations are permitted during the first 4 weeks of the treatment period. Every effort should be made that the highest tolerated dose is reached on visit 1, at the latest, and only down-titrations are done after that, if clinically indicated. If dose is modified (down- and/or up-titrated) within the first 4 weeks, an unscheduled visit should be performed to assess subject safety on the new dose level. As dose modifications may be performed at any visit, the subjects will be asked to return their study medication at each site visit. They will be given new study drug packages or the same study drug packages will be returned to them, as applicable, according to the investigator's decision on dose modification.

The subjects will have to be on a stable dose of study treatment for a minimum of 6 weeks before visit 3. Visit 3 will include safety assessments (BP and safety laboratory tests), blood samples will be obtained for biomarker analysis and PET-scan and echocardiography will be performed. Before the PET-scan, a urine pregnancy test should be performed for female subjects of childbearing potential. The study ends for a subject after the last assessment is performed during visit 3; there will be no separate end-of-study visit. The subject will return the study medication to the site and he/she will continue his/her normal HF therapy, as advised by the investigator.

Adverse events and changes in concomitant medications will be recorded throughout the treatment period. Any possible serious adverse events (SAEs) or other clinically significant AEs, as judged by the investigator, will be followed up after the last study visit until resolution or until the event is considered chronic and/or stable.

7.3 Unscheduled visits

Unscheduled visits may occur at any time during the study, if considered necessary by the investigator. The main purpose of an unscheduled visit will be to assess subject safety and any safety-related study assessment(s) may be performed during this visit, including BP and HR measurement and safety laboratory tests. In addition, AEs and concomitant medications may be reviewed by the investigator. If necessary, changes to the subject's concomitant medication or study treatment (e.g. down-titration) may be performed.

8 ASSESSMENTS

8.1 Screening data

Information to be recorded during the screening/run-in period includes demographic and other baseline information (Section 8.1.1) and safety laboratory determinations (Section 8.1.2).

8.1.1 Demographic and other baseline information

The following demographic and other baseline information will be collected:

- subject's name, address, contact information (not on CRF);
- year of birth
- race;
- information on relevant previous diseases and current medical conditions;
- information on previous and current medications; all treatments used (including prescription medications, over-the-counter medications, herbal remedies, trace elements and vitamins) within 4 weeks before the screening visit will be recorded;
- information on previous participation in clinical trials;
- systolic and diastolic BP and HR is recorded in a seated position after at least 5 min of rest;
- blood samples are collected for safety laboratory determinations;
- personal identity number is collected (not on CRF) due to laboratory logistics, on subject's permission given in the ICF;

8.1.2 Screening laboratory determinations

All subjects will undergo blood laboratory tests during the screening/run-in period on screening visits 1 and 2. The reference ranges of all laboratory determinations will be included in the ISF before study start and updated whenever necessary. The laboratory tests detailed below are taken during the screening visits:

Chemistry:

- Potassium
- Creatinine

Haematology:

- Haemoglobin

8.2 Assessment of efficacy

In order to assess cardiac efficiency and hemodynamics, PET imaging and echocardiography will be performed before randomization (after a minimum of 4 weeks on stable dose of 80 mg BID or 160 mg BID of valsartan) and repeated after 6 weeks on a stable dose of either 80 mg BID or 160 mg BID of valsartan or 100 mg BID or 200 mg BID of sacubitril/valsartan.

8.2.1 ^{11}C-acetate PET- scan

Myocardial resting perfusion and oxygen consumption will be evaluated by ^{11}C-acetate PET as tracer uptake (k_1) and a mono-exponential clearance rate of ^{11}C-acetate (k_{mono}) before randomization and repeatedly on visit 3, after 6 weeks of stable sacubitril/valsartan or valsartan treatment. Resting perfusion (k_1) will be used for calculation of myocardial vascular resistance. Efficiency of LV mechanical work will be calculated as follows:

Efficiency = (LV work/gram of tissue) / Oxygen consumption

PET-imaging will be performed using a PET scanner (GE Discovery 690PET/CT) at [redacted].

8.2.2 Echocardiography

Comprehensive echocardiographic evaluation of cardiac structure, systolic function, diastolic function using 2D and 3D imaging, strain imaging and Doppler will be done before randomization and repeatedly on visit 3, after 6 weeks of stable sacubitril/valsartan or valsartan treatment. Estimates of LV filling pressure will be used to assess hemodynamic effects of interventions. Measurements of LV mass (linear method), LV outflow tract (LVOT) area and cardiac output (Doppler flow velocity profiles in the LVOT or LV volumes) will be used for calculation of LV mechanical work as follows:

LV work/gram of tissue= (SBP x SV x HR) / LV mass;

where SBP is systolic blood pressure, SV is stroke volume and HR is heart rate.

Echocardiography will be performed using a GE Vivid E9 ultrasound machine. Separate written instructions will be provided to the study team before the start of the clinical part of the study with detailed description on the PET procedure and echocardiography.

8.2.3 Biomarkers

Biomarkers will be measured to understand the potential mechanisms of how sacubitril/valsartan changes myocardial efficiency. Blood samples will be obtained for measurement of NT-proBNP, hs-troponin and creatinine to assess effects of interventions on hemodynamics before randomization and repeatedly on visit 3, after 6 weeks of stable sacubitril/valsartan or valsartan treatment. The biomarker analyses will be performed at [redacted], the accredited clinical laboratory of [redacted]

In addition, one blood sample will be taken and stored up to 15 years for possible future biomarker analysis.

8.3 Assessment of safety

8.3.1. Physical examination

Physical examination will include the examination of general appearance as well as the cardio-vascular system as seen relevant by the investigator, for example lungs, heart and extremities.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present before signing the ICF must be included in the relevant medical history eCRF. Significant findings made after signing the ICF which meet the definition of an AE must be recorded in the Adverse Event eCRF.

8.3.2 Blood pressure and heart rate

BP and HR will be measured in a seated position after at least 5 min rest at all site visits for safety assessment. BP and HR will be monitored also during the imaging sessions according to separate written instructions. SVR will be calculated based on peripheral BP and cardiac output.

In case of abnormal findings, additional control assessments may be performed according to investigator’s judgement.

8.3.3 Laboratory safety assessments

Please refer to Section 8.1.2 for laboratory safety assessments to be performed during the screening visits. During the treatment period on visits 1-3, the same laboratory assessments will be performed, and also on unscheduled visits, if clinically indicated. Safety blood samples may be collected 1-2 business day(s) before the scheduled visits (with the exception of screening visit 1). If necessary to assess subject safety, more laboratory tests may be performed at any visit. In this study, the maximum volume of blood drawn from a subject for safety laboratory assessments during scheduled visits will not exceed 50 ml. If control blood samples are needed for subject safety, the blood volume may exceed 50 ml. The analyses of clinical chemistry will be performed at [redacted], the accredited clinical laboratory of [redacted].

Urine pregnancy test will be performed for all female subjects with childbearing potential prior to the PET-scans. Urine pregnancy test will be performed at [redacted] using available commercial kits.

The investigator will evaluate the clinical significance of the safety laboratory findings. In case of abnormal findings, additional control assessments may be performed according to investigator's judgement. For specific laboratory values resulting in subject withdrawal, please refer to Section 5.8.

8.3.4 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study until the end of study. 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. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

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

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

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

the responsibility for managing the safety of individual patient and identifying adverse events.

Adverse events must be recorded in the appropriate CRF capturing AEs 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
- 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 8.3.3.1.1 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding [investigational] treatment

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

- no action taken (e.g. further observation only)
- [investigational] treatment dosage increased/reduced
- [investigational] treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 8.3.3.1.1 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.

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.

8.3.4.1 Serious adverse events

8.3.4.1.1 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
  - 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.

8.3.4.1.2 SAE reporting

IMPORTANT: To comply with regulations, all suspected, unexpected, serious adverse reactions (SUSARs) occurring in a clinical trial must be reported in an expedited timeframe (7 or 15 days) to competent authorities.

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 safety within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis safety if the investigator suspects a causal relationship to study treatment.

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

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

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the 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 Patient Safety 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 and as per national regulatory requirements in Finland.

Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

8.3.4.2. 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 category of abnormalities / adverse events has to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

- Liver events, which will require close observation, follow-up monitoring should be entered into the appropriate CRFs.

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 the appropriate CRFs.

8.3.4.3 Renal safety monitoring

The following category of abnormal renal laboratory value has to be considered during the course of the study:

- Serum event:
  - confirmed (after ≥24h) increase in serum creatinine of ≥25% compared to baseline during normal hydration status

8.3.4.4 Reporting of study treatment errors including misuse/abuse

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

Medication errors are usually unintentional, although a patient can intentionally 'commit' a medication error due to a lack of medical knowledge or sound judgment (e.g. intentionally removing drug from capsule and dissolving in juice) or there is an accidental drug omission by an HCP).

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 appropriate CRF, 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 4. Guidance for capturing the study treatment errors including misuse/abuse

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

8.3.4.5 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.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Patient Safety. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment. Pregnancy should be followed up until the child is born and until all relevant information related to the child's condition has been received.

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

8.3.4.6. Serious adverse event reporting

In case of an SAE, the investigator will contact the Sponsor as soon as possible. SAEs must be reported to Novartis' local Patient Safety within 24 hours of becoming aware of an SAE, regardless of the time that may have elapsed since the time the event occurred and regardless of the causal relationship of the study drug to the event. An initial SAE report will be submitted by the investigator to the Sponsor, and follow-up reports will be provided later, if indicated. Follow-up reports to an SAE should be prepared if any relevant change in the condition of the study subject occurs after the initial report. SAEs should be followed up until resolved or until the event is considered chronic and/or stable outcome.

The contact person(s) and address of the Sponsor for SAEs is(/are):

Novartis Patient Safety Finland

[redacted]

Tel. [redacted]
e-mail: [redacted]
Fax: [redacted]

Novartis Local Patient Safety is responsible for forwarding the SAE report(s) to the global Patient Safety and for ensuring that the reports are submitted to Eudravigilance, if applicable, according to local laws and regulations and Novartis internal guidelines.

To ensure that there is no SAE unreported or not registered into the study database, a reconciliation process is to be set up between the sponsor [redacted] before the study start. During the study, the local Patient Safety is responsible to send once a month a list to [redacted] with all received SAEs from the study. [redacted] confirms by email to local Patient Safety that there was no additional SAEs sent to Patient Safety for further processing. If any discrepancies are identified, corrective actions have to be taken.

DM is to reconcile SAEs registered in the clinical database against the SAEs registered with the Novartis global database on a regular basis. Prior to last subject's last visit (LSLV), [redacted] DM is to order the complete list of reported SAEs to the Sponsor in order to ensure that all the study SAEs have been reconciled appropriately. From LSLV onwards, no new SAEs occurring or follow-up information for existing SAEs received after LSLV, will be reconciled.

Suspected Unexpected Serious Adverse Reactions

An unexpected adverse drug reaction is any ADR, the specificity or severity of which is not consistent with the current SPC of sacubitril/valsartan. Suspected unexpected serious ADRs (SUSARs) are subject to expedited reporting to the CA. The Sponsor reports all authority-reportable AEs to the CA.

The global Novartis Patient Safety produces bi-annual blinded SUSAR listings that are provided to the investigators. The study monitor verifies that the listing has been received, signed and dated by the PI and that it has been filed in the ISF.

In addition, progress and final study reports will be included or updated in the corresponding periodic safety update report (PSUR), which is compiled and provided by Novartis. The study MA is responsible for sending a report on study progress at least annually to global program medical director and to Country Patient Safety Heads. The report should include all relevant data e.g. numbers of patients, problems encountered and deviations from expected plan etc. upon completion of the study.

Novartis prepares molecule specific DSURs (Development Safety Update Reports) annually for HA and EC submissions. With this report the Finnish HA and ECs require a written statement concerning safety of the Finnish trial subjects during the report period. It is a responsibility of the NCI to write this statement within the requested timelines.

9 STATISTICS

9.1 Estimation of sample size

In previous studies using the same techniques (i.e. ^{11}C-acetate PET scan and echocardiography), beta-blockers in drug-naïve patients increased cardiac efficiency by 45% (Beanlands 2000). In later studies using e.g. new biventricular pacing techniques in previously medicated patients, the cardiac efficiency was improved by 20% (Sundell 2004). Therefore, we assume that the clinically significant change in cardiac efficiency in medicated patients would be about 20%. In our previous studies in patients with heart failure (Nesterov 2015, Tuunanen 2008), the same patients were studied twice in the interval of 3 months, the coefficient of variation (CV%) of K_{mono} in placebo group was 18.4% and in efficiency 19.7%. Based on sample size calculations, in order to detect a 15% change in cardiac efficiency, 27 subjects would need to be included in each treatment arm (assuming $\alpha = 0.05$ and $\beta = 0.2$). Due to potential drop outs during the study, the target is to enroll 30 + 30 subjects in the treatment arms.

9.2 Statistical methods

A summary of the statistical methods is described below.

9.2.1 Statistical Analysis Plan

Before unblinding the study data a separate statistical analysis plan (SAP), which will provide the technical details of the statistical analysis outlined below, will be prepared by the biostatistics service provider, and approved.

9.2.2 Statistical hypotheses

The study hypothesis is that short-term therapy with sacubitril/valsartan added on standard HF therapy improves cardiac efficiency in patients with systolic HF. In order to test this, the null hypothesis is formulated as follows:

$$H_0 : \mu_1 = \mu_2$$

which will be tested against the alternative hypothesis:

$$H_A : \mu_1 \neq \mu_2$$

where μ_1 and μ_2 are the mean values of change in cardiac efficiency in the two treatment arms, as measured by PET and echocardiography at visit 3. The null hypothesis will be tested based on a two-sided test and a significance level of 0.05.

9.2.3 Data sets to be analyzed

The following analysis sets will be used for the statistical analysis and presentation of data:

The safety set will consist of all randomised subjects who received at least one dose of the study medication in the treatment period, provided that there was at least one safety follow-up performed for the subject.

The full analysis set (FAS) will consist of all randomised subjects who have received at least one dose of study medication in the treatment period and have at least one post-baseline assessment of any efficacy endpoints.

The per protocol set (PPS) will consist of all subjects in the FAS who received at least 75% of the study drug doses, and do not have any other major protocol violations which will affect the assessment of efficacy. Major/important protocol violations may include, but are not limited to, the following:

- Non-fulfillment of all inclusion criteria
- Fulfillment of at least one exclusion criteria
- Use of certain concomitant medications (this will be judged on a case to case basis, depending on extent of treatment)

The final criteria for PPS, regarding which protocol deviations that warrant exclusions, will be determined when all data on protocol violations/deviations are available and before breaking the blind. The FAS is considered as the primary analysis dataset, and will be used for all primary and secondary efficacy analyses. The primary efficacy analysis will be repeated using the PPS. Any significant discrepancy between the results from the FAS and the PPS will be analysed and discussed.

Baseline presentations will be based on the safety set.

Safety presentations will be based on the safety set

9.2.4 General statistical considerations

All data will be analyzed using summary statistics and listed. Summary statistics will include at least the number of subjects, mean, standard deviation, median, minimum and maximum for continuous variables, and frequencies and percentages for categorical variables. Geometric mean, standard deviation and coefficient of variation will also be presented, when appropriate. All summary statistics will be presented by treatment and dose level. All data collected will be listed by subject and dose level. In addition, analysis of covariance (ANCOVA) will be used for statistical analysis, when appropriate. Other statistical analyses may also be implemented, as described in the SAP.

9.2.5 Demographic and baseline characteristics

All relevant demographic and baseline characteristics will be summarized using descriptive statistics. The number and reasons for withdrawals and discontinuations

will be listed and tabulated by treatment and dose level. Separate listings will be provided for subjects screened but not included in the study (screening failures).

9.2.6 Analysis of efficacy variables

All efficacy variables will be tabulated using summary statistics as described in section 9.2.4, including both statistics for observed levels by visit and changes from baseline.

Primary Endpoint

The primary endpoint, change from baseline in cardiac efficiency after 6 weeks on stable sacubitril/valsartan or valsartan therapy, will be analyzed by an ANCOVA including treatment and stratification as independent factors and covariate adjustment for baseline cardiac efficiency. From this model, the within treatment group (sacubitril/valsartan-valsartan) changes will be estimated by least square means and the corresponding treatment difference between treatments will be calculated with a 95% confidence interval and p-value. In addition, treatment by stratification interaction analyses will be performed for the primary efficacy parameters in order to estimate within stratification group differences. For both the baseline visit and visit 3, the results will be also summarized using descriptive statistics, with the visit 3 results to be summarized also by dose level and treatment arm.

Exploratory Endpoints

The changes in the following cardiac and systemic hemodynamics parameters will be evaluated as exploratory efficacy endpoints: EF, NT-proBNP, systemic BP, SVR, coronary vascular resistance and cardiac oxygen consumption. The change from baseline in these parameters after 6 weeks on stable sacubitril/valsartan or valsartan therapy will be analyzed by an ANCOVA including treatment and stratification as independent factors and covariate adjustment for baseline cardiac efficiency. From this model, the within treatment group (sacubitril/valsartan-valsartan) changes will be estimated by least square means and the corresponding treatment difference between treatments will be calculated with a 95% confidence interval and p-value. For both the baseline visit and visit 3, the results will be also summarized using descriptive statistics, with the visit 3 results to be summarized also by dose level and treatment arm.

9.2.7 Analysis of safety variables

9.2.7.1 Evaluation of adverse events

AEs reported during the study will be classified by system organ class (SOC) and preferred terms (PT) using the MedDRA coding system. AEs will be displayed in a frequency table by dose level and treatment arm. The number and proportion (%) of subjects having each AE will be tabulated by SOC and PT and dose level. Severity of the AEs (mild, moderate, severe) and causality to the study treatment will be

tabulated with subject and event counts. SAEs and other significant AEs will be evaluated case by case.

AEs occurring before and after the initiation of the double-blind treatment period will be reported separately.

9.2.7.2 Clinical safety evaluations

The actual values of systolic and diastolic BP and HR and their changes from baseline will be evaluated with descriptive statistics by dose level and treatment arm. There will be two separate baseline values defined for the BP and HR measurements: the first BP and HR baseline value will be the one taken on the first screening visit. The subsequent BP and HR measurements during the screening/run-in period will be compared to this. The second baseline value will be the one taken before randomization at the baseline visit. The subsequent BP and HR measurements during the double-blind treatment period will be compared to this.

9.2.7.3 Clinical safety laboratory evaluations

All laboratory safety variables and their changes from baseline will be evaluated and summarized using descriptive statistics by dose level and treatment arm. There will be two separate baseline values defined for the safety laboratory assessments: the first safety laboratory baseline values will be the ones taken on screening visit 1. The subsequent laboratory results obtained during the screening/run-in period will be compared to these. The second safety laboratory baseline values will be the ones taken at the baseline visit. The subsequent laboratory results obtained during the double-blind treatment period will be compared to these. Laboratory values will also be categorized into low, normal and high according to their reference ranges. Clinically significant laboratory abnormalities and any additional laboratory tests taken for subject safety will be listed and reported in the study report.

9.3 Interim analyses

There will be no planned interim analyses during the study. The investigators and the sponsor will monitor subject safety and efficacy results on an ongoing basis.

9.4 Software

Statistical analysis will be performed and tables and subject data listings will be prepared using SAS®.

10 DATA MANAGEMENT

Data management and handling of data will be conducted according to the study-specific Data Management Plan (DMP) in line with ICH guidelines [redacted] standard operating procedures.

10.1 Database design

The trial database and data entry screen design, as well as edit checks will be defined according to the corresponding eCRFs and the study protocol.

10.2 Data entry

Flow of trial data and procedures regarding data handling will be described in detail in the DMP. Data will be collected on eCRFs specifically designed for this study. eCRF completion guidelines will be provided to enable accurate data entry.

The investigator or designated study center personnel will enter subject data into the eCRFs. Only persons authorized by the investigator to make original eCRF entries will be allowed to make corrections. The eCRF will have an audit trail with appropriate functionality for data capture, tracking and documentation of any queries or changes. Electronic signatures will be used to lock the data and identify the person entering or changing the data.

All eCRF entries should be verifiable from the study records. Definition of source data is agreed in a written source data agreement document before study start.

Authorized persons will code medical history and current medical conditions, AEs and concomitant treatments using standard coding dictionaries.

10.3 Data validation and query management

Data validation or data cleaning procedures will be designed to assure the validity and accuracy of the study data. A Data Validation Plan will specify the data checks that are performed on subject data to raise data discrepancies, and define the electronic edit checks, and data validation queries created for the trial. Validation and data queries will be handled by [redacted] DM team. All trial specific and standard data validation programming will be tested in a separate testing environment prior to use on production data.

10.4 Medical encoding

AEs and medical history verbatim terms will be encoded using MedDRA, latest version available when approving the DMP. Concomitant Medications verbatim terms will be encoded using the World Health Organization Drug Dictionary (WHO DD), most recent version held by the DM vendor.

10.5 Data lock

Individual pages in the eCRFs may be locked on an ongoing basis during the study. A field may be locked after all necessary actions defined for that particular field have been completed. The fields may be unlocked if further updates are needed.

10.6 Database closure

All data entry, verification, medical encoding and data validation activities will be finalized before final database lock. Quality control activities will be completed to acceptable error rates. All unnecessary user privileges to the study data will be removed, except for the Data Manager who will perform the database closure. Before database closure reconciliation will be performed between the SAEs entered in the Safety database and the study database. After database closure, the database will be exported as SAS® data sets.

The locked database will be used in the final statistical analyses for study reporting. Any deviations, i.e. discrepancies and additions from the process defined in the DMP, will be described in a study specific Data Management Report.

10.7 Software

TrialOnline will be used for DM.

11 QUALITY CONTROL AND QUALITY ASSURANCE

The principles of GCP are followed throughout the study. During the PET scans, the SOPs of [redacted] are followed and for DM and statistics, the SOPs of [redacted] are followed. [redacted] Laboratory quality certificates will be available prior to study initiation and will be filed in the ISF and TMF.

The study will be monitored by [redacted] The study monitor is allowed to monitor the study as frequently as necessary to ensure that data recording and protocol adherence are satisfactory. The CRFs and related source data will be reviewed in detail and source data verification will be performed according to the monitoring plan.

The quality assurance personnel [redacted] and the Sponsor may conduct audits in any phase of the study. The study may also be inspected by CAs.

A curriculum vitae in English will be obtained from all investigators who sign the protocol and from other relevant persons.

12 ETHICAL CONSIDERATIONS

This study will follow the relevant regulations and guidance for biomedical research involving human subjects, such as the Declaration of Helsinki, GCP, national laws and EU directives. Special emphasis will be put on the well-being of the study subjects.

Prior to initiation of the study, the study protocol, the subject information leaflet and the ICF, the Description of the Study Data Register and the texts of any advertisements used for the recruitment of study subjects will be submitted to and approved by an independent EC. The EC will also be notified of any other materials to be given to the subjects (*e.g.* study subject diary, participant card). The study will be authorized by the CA (the Finnish Medicines Agency, Fimea) before its commencement.

The study subject candidates will be provided with both verbal and written information on the study, its risks and benefits. They are encouraged to ask questions on the study. After having had enough time to consider their participation, they may sign the IC form. No study procedure will be implemented prior to obtaining written IC that is signed by the subject at the time of consent. A copy of the signed ICF will be given to the subject. The investigator will keep each subject's signed ICF on file for inspection by a regulatory authority at any time.

The subjects are told what information will be collected of them and how. The collection of study data and its confidential storage are described in the Description of the Personal Data Register, which is kept in the ISF and is available for inspection by the subjects. The investigator assures that the privacy of the subjects, including their personal identity and all medical information, will be maintained at all times.

This study involves exposure to ionizing radiation, which is harmful to living organisms. The total radiation dose from two up to 500 MBq ^{11}C-acetate PET tracer injections and low-dose CT scans for attenuation correction will be 7.5 mSv. The average annual radiation dose of a person living in Finland derived from the environment and from medical uses of radiation is approximately 3.2 mSv per year (Radiation and Nuclear Safety Authority of Finland). Therefore, the radiation exposure from this study will be approximately equivalent to 2 years and 4 months of background radiation in Finland. Despite the ionizing radiation exposure being low, any radiation dose may increase the risk of cancer.

Other invasive procedures included in the study are the frequent blood samplings. The volume of blood drawn from each subject during the scheduled visits will not exceed 50 ml. This blood loss should not produce any adverse effects. Echocardiography is a non-invasive ultrasound-based imaging method used to assess cardiac function that is not associated with any known safety risks.

The subjects are urged to report all AEs to the study personnel and they are given the phone numbers of the investigator and study nurse(s) whom they are instructed to call if they observe significant, possibly study drug related AEs, or in other urgent study-related issues.

The subjects included to this study will have chronic HF, NYHA II-III symptoms and reduced EF. Their ongoing HF treatment will not be modified, with the exception of

changing their ACEI or ARB medication to valsartan during the screening/run-in period. The medication change and subsequent possible up-titration will be closely monitored by the study team to ensure subject safety at all times. During the double-blind treatment period, subjects will receive either sacubitril/valsartan or valsartan and are expected to remain in a stable clinical condition. Also during this period, possible up-titration(s) will be closely monitored by the study team. In addition to the above mentioned medication changes, the study protocol allows for down-titration of a loop diuretic, if indicated based on clinical signs and/or symptoms. This study is designed so that the health and safety of the subjects can be monitored as closely as possible.

Substantial changes to the final approved study protocol will be initiated only with the EC's favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the study subjects. When a change involves only logistics or administration, it will be considered non-substantial, and needs not be submitted to the EC or the CA for approval. The CA will also be notified before adopting a substantial amendment.

After the study has been completed and a Clinical Study Report prepared, the EC and CA will be notified as agreed by the Sponsor [redacted].

13 DATA HANDLING AND RECORD KEEPING

13.1 Case report forms

Data to be collected according to the study protocol (and its amendments, if any) shall be recorded on study-specific eCRFs generated by [redacted] The data will be recorded with electronic data capture (EDC) using eCRFs at the study center. All data on the CRFs must be verifiable in the source data unless declared as source data in the monitoring plan.

CRFs are required for each study subject. They will be completed in English by the investigator or other authorized study personnel. The investigator has to confirm the content of the CRF by an electronic signature.

Corrections to the CRFs may be made by the investigator or other authorized study personnel. An audit trail within the system will track all changes/corrections made.

Instructions and training for completing the CRFs will be provided. These instructions will cover the content and technical issues of the EDC system.

13.2 Source data

Source data will recorded in the study subject's medical records. Access to the source data revealing the identity of the study subjects is only to the study personnel and study monitor. The generated source data are stored at [redacted], [redacted].

The laboratory results of the blood safety determinations and biomarkers are stored as print-outs within the ISF and in the patient records of [redacted] the personnel of which is bound to professional secrecy.

13.3 Deviations

In case the study monitor, the investigator, a study nurse or other authorized person involved in the study observes a protocol deviation or discrepancy, he/she should describe the issue as clearly as possible in a written memorandum. In addition to the date and signature of the writer, the investigator, the monitor or an authorized Sponsor's representative will also sign the memorandum. Deviations concerning a single subject will be described in the corresponding CRF.

13.4 Amendments

Minor changes (*e.g.*, concerning logistics or administration) to the clinical study protocol can be clarified in a memorandum or in a non-substantial amendment, if the change has no effect on the safety of the subjects or on the scientific value of the study. The investigator will inform the Sponsor of such minor changes. All essential changes to the clinical study protocol are described in a substantial amendment, which is submitted for approval by the EC and CA before adopting the changes, except when necessary to eliminate immediate hazards to the study subjects. Amendments to the clinical study protocol are prepared as agreed by the parties involved in the study.

14 STUDY SCHEDULE

The study is planned to be carried out Q3/2017 – Q2/2019.

15 CRITERIA FOR PREMATURE STUDY TERMINATION

The study may be discontinued at the clinical site at the discretion of the Principal Investigator and/or the Sponsor based *e.g.* on the occurrence of the following:

- ADRs unexpected to date in respect to their nature, severity, and duration or the unexpected incidence or severity of expected ADRs.
- Medical or ethical reasons affecting the continued performance of the study.
- Difficulties in the recruitment of subjects.
- Significant deviations from the protocol.

The investigator will inform the EC and the sponsor will inform the CA if the study is terminated prematurely. The Sponsor reserves the right to prematurely terminate the study for valid scientific or administrative reasons. In the case of premature termination of the study, the investigator will proceed to appropriate actions (described in a separate memorandum) concerning the study subjects.

16 FINANCING AND INSURANCE

Financial matters related to the study are covered by an agreement between [redacted] the Sponsor, and in appropriate agreements between any other relevant parties of the study. The Sponsor has an insurance policy covering damages caused by the investigational products administered during the study. The insurance statement will be provided in the ISF and TMF. In case of any injury caused by an incident that is related to the study procedures but is not causally related to the investigational products, study subjects will be covered by the patient insurance of [redacted].

17 STUDY REPORT AND PUBLISHING

A final Clinical Study Report will be prepared after the study has been completed or prematurely terminated. The Sponsor may submit the report to another party. The EC will be notified by [redacted] while the CA will be notified by the sponsor about study completion according to applicable laws and regulations. The study report will be approved by the principal investigator and the Sponsor. The Sponsor remains the exclusive owner of the study data defined in the protocol. All involved parties agree that the study results should be published according to usual scientific practice. The eventual publication of the study results and authorship of the eventual publication(s) will be mutually agreed. Manuscripts will not be submitted for publication without prior approval of the Sponsor.

18 ARCHIVING

The ISF (including *e.g.* source data, subject screening and identification logs, original signed ICFs, copies of CRFs, and drug accountability records) will be archived by study site to enable possible follow-up assessments or audits by the Sponsor, or inspections by regulatory authorities. The ISF is archived for at least 15 years after the end of the study, unless specified otherwise by a written agreement between the Sponsor and study site. The study site may lend materials of this study to third parties on the Sponsor's documented permission.

The Sponsor will archive the TMF according to applicable laws and regulations. Information collected during the course of this study will be stored by the Sponsor and used in the further development and understanding of the study drug for as long as the information is relevant for patient care. Its use includes the transfer of data to regulatory authorities of the European Union or its member or affiliated states (*i.e.* non-EU countries belonging to the European Economic Area, EEA), the USA or other non-EU/EEA countries for the purpose of obtaining, maintaining and processing of marketing authorizations. All information is handled confidentially and according to the current laws and regulations.

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20 APPENDICES

Appendix 1. Subject information sheet and Informed consent form
Appendix 2. Signed consent of the investigator(s)