Official Title:	**A Randomized, Double-blind, Active-controlled Study to Assess the Effect of Sacubitril/Valsartan Compared With Enalapril to Improve Erectile Function in Patients With Heart Failure With Reduced Ejection Fraction and Erectile Dysfunction**
NCT Number:	NCT03917459
Document Dates:	Original Protocol : 07 August 2018 Protocol Version 01: 15 January 2019

Appendix 16.1.1 Protocol and protocol amendments

History of changes	
Version	**Summary of changes**
1.0	Original version

1 Protocols and protocol amendments

Table 1-1 List of protocols, protocol amendments and post text supplements

Document	Effective Date
Original Protocol	07-Aug-2018
[redacted]	[redacted]
Amended Protocol Version 01 (clean version)	15-Jan-2019

NOVARTIS

Global Clinical Development - General Medicine

sacubitril/valsartan

Clinical Trial Protocol CLCZ696BDE03

A randomized, double-blind, active-controlled study to assess the effect of sacubitril/valsartan compared with enalapril to improve erectile function in patients with heart failure with reduced ejection fraction (HFrEF) and erectile dysfunction (ED)

Document type:	Clinical Trial Protocol
EUDRACT number:	2018-000220-33
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Clinical trial phase:	IV
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List of abbreviations

ACE	Angiotensin-converting-enzyme
ACEI	Angiotensin-converting-enzyme inh bitor
AE	Adverse Event
ALT	Alanine aminotransferase
ANP	Atrial natriuretic peptide
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
bid	twice a day
BNP	Brain natriuretic peptide
BUN	Blood urea nitrogen
cGMP	Cyclic guanosine monophosphate
cHF	Chronic heart failure
CNP	C-type natriuretic peptide
CPK	Creatine phosphokinase
CPO	Country Pharma Organization
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTRD	Clinical Trial Results Database
d	day
ED	Erectile dysfunction
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
eGFR	Estimated glomerular filtration rate
EOS	End of study
eSource	Electronic Source
GC	Guanyl cyclase
GCP	Good Clinical Practice
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IIEF	International Index of Erectile Function
INR	International normalized ratio
i.v.	intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
LFT	Liver function test
LVEF	Left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
Mg	Milligram

mmHg	Millimeter mercury
MRA	Mineralocorticoid Receptor Antagonist
NEP	Neutral endopeptidase/neprilysin
NO	Nitric oxide
NYHA	New York Heart Association
od	once a day
pGC	particulate guanyl cyclase
p.o.	oral(ly)
PSD	Premature subject/patient discontinuation
QoL	Quality of Life
RAAS	Renin angiotensin aldosterone system
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SMC	Smooth muscle cell
SmPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total bilirubin
TD	Study Treatment Discontinuation
UACR	Urinary albumin to creatinine
ULN	Upper limit of normal
w	Week(s)
WBC	White blood cell
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of patients/subjects fulfilling certain criteria
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
eSource DDE	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications reduce the use of paper capture source data during clinical visits. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures descr bed in the protocol)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”.
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients/subjects with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug(s), placebo/comparator active drug run-ins or background therapy

Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Protocol summary

Protocol number	CLCZ696BDE03
Full title	A randomized, double-blind, active-controlled study to assess the effect of sacubitril/valsartan compared with enalapril to improve erectile function in patients with heart failure with reduced ejection fraction (HFrEF) and erectile dysfunction (ED)
Brief title	COmparing arNi and ace For Improving erectile Dysfunction in mEN with reduCed Ejection fraction heart failure
Sponsor and Clinical Phase	Novartis Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Heart failure (HF) patients typically display various symptoms including peripheral congestion, low exercise tolerance, fatigue and dyspnea, which contribute to a progressive worsening of quality of life (QoL). Additionally, sexual activity remains an essential aspect of QoL, since, contrary to common belief, seriously ill patients mostly do not lose their interest in intimacy. An estimated 70% of male HF patients experience erectile dysfunction (ED). Decreasing left ventricular function is associated with significantly reduced erectile function in cardiovascular high-risk patients and ED was shown to precede cardiovascular events in these patients. A secondary analysis of the Kansas City Cardiomyopathy Questionnaire (KCCQ) used in the PARADIGM-HF trial demonstrated that patients treated with sacubitril/valsartan significantly improved nearly all criteria at the physical limitation and social limitation section when compared with enalapril, with the most significant changes in intimate/sexual relationships after 8 months of double-blind treatment. Based on these beneficial effects and the potential positive influence of enhanced CNP levels under sacubitril/valsartan treatment in erectile tissue, we hypothesize that sacubitril/valsartan may also enhance erectile function in male HFrEF patients, thereby contributing to improvement of QoL. Enhancement in erectile function will be evaluated using the renowned International Index of Erectile Function (IIEF).
Primary Objective(s)	To demonstrate the superiority of sacubitril/valsartan compared to enalapril regarding improvement in erectile function and ability in

	male patients with chronic heart failure and erectile dysfunction using the questionnaire International index of erectile function (IIEF-15) at the end of the study.
Secondary Objectives	• To assess the early-onset effect as well as the effect at the end of the study of sacubitril/valsartan versus enalapril regarding improvement in sexual activity assessed using patient's self-reported frequency of sexual activity per month • To assess the early-onset effect as well as the effect at the end of the study of sacubitril/valsartan versus enalapril regarding NT-proBNP levels
Study design	This is a randomized, double-blind, double-dummy, multi-center, active-controlled, interventional study to compare sacubitril/valsartan to enalapril in improving erectile function in male patients with chronic heart failure (NYHA II) and reduced ejection fraction (HFrEF) and erectile dysfunction (ED).
Population	The study population will consist of a representative group of adult (≥18 and ≤ 75) male HFrEF patients in NYHA class II with mild to moderate ED. Eligible patients should be on a stable dose of an ACEI or an ARB as well as bisoprolol/metoprolol for at least 4 weeks prior to randomization. The targeted projected sample size is 200 patients (100 patients in each arm). It is expected that 286 patients will be screened at up to approximately 40 study sites, as a screen failure rate of 30% is anticipated.
Key Inclusion criteria	• Patients must give written informed consent before any assessment is performed and must be willing and capable to comply with all study procedures • Male Outpatients ≥ 18 and ≤ 75 years of age • Patients with a diagnosis of CHF NYHA class II and reduced ejection fraction (< 40%) at Visit 1 • Plasma NT-proBNP level of ≥ 300 pg/mL at Visit 1(Screening) • Patients must be living in a stable and sexually active heterosexual partnership for at least 6 months prior to Visit 1 • Patients must have a mild to moderate erectile dysfunction determined using the IIEF-5 questionnaire (> 7 and ≤ 21 IIEF units) at Visit 1 (Screening) and Visit 2 (Randomization) • Patients must be on an ACEI or ARB at a stable dose for at least 2 weeks prior to Visit 1 and 4 weeks prior to Visit 2 • Patients must be treated with a stable dose of bisoprolol/metoprolol for at least 2 weeks prior to Visit 1 and 4 weeks prior to Visit 2 • No usage of any available drug for erectile dysfunction (e.g. sildenafil, tadalafil) for at least 2 weeks prior to Visit 1 and 4 weeks prior to Visit 2

Key Exclusion criteria	• History of hypersensitivity or allergy to any of the study drugs, drugs of similar chemical classes, ACEIs, ARBs, or NEP inhibitors as well as known or suspected contraindications to the study drugs • Previous history of intolerance to recommended target doses of ACEIs or ARBs • Known history of angioedema • Requirement of treatment with both ACEIs and ARBs • Current acute decompensated HF (exacerbation of chronic HF manifested by signs and symptoms that may require intravenous therapy) • Symptomatic hypotension and SBP ≤100 mm Hg at Visit 1 (Screening) or Visit 2 (Randomization) • Estimated glomerular filtration rate (eGFR) below 30mL/min/1.73m^2 at Visit 1 (Screening) or Visit 2 (Randomization) • Serum potassium level of more than 5.2 mmol/L at Visit 1 (Screening) or Visit 2 (Randomization) • History of severe pulmonary disease • Penile anatomical defects and Peyronie's disease • Foreseeable usage of any available drug for erectile dysfunction (e.g. sildenafil, tadalafil) during the trial • Prostate-specific antigen (PSA) levels higher than 4 ng/mL at Visit 1 or known prostate cancer
Study treatment	• Sacubitril/valsartan (target dose 97 mg/103 mg bid) • Placebo to match sacubitril/valsartan at all dose levels • Enalapril (target dose 10 mg bid) • Placebo to match enalapril at all dose levels
Efficacy assessments	• IIEF-15 questionnaire • Patient-reported frequency of sexual activity • Changes in NT-proBNP [redacted]
Key safety assessments	• Adverse event monitoring • Physical examinations and blood pressure monitoring

	• Monitoring of laboratory markers in blood (potassium, creatinine, AST/ALT)
Other assessments	Not applicable
Data analysis	The primary variable will be analyzed using a mixed model for repeated measures (MMRM). The response variable will be the Erectile function score IIEF-15. Treatment (sacubitril/valsartan versus enalapril), visit and treatment-by-visit interaction will be included as fixed-effect factors; baseline IIEF-15 will be included as a covariate. Secondary endpoints will be analyzed descriptively.
Key words	Erectile dysfunction, heart failure, reduced ejection fraction, sacubitril/valsartan, enalapril, randomized controlled trial

1 Introduction

1.1 Background

Heart failure (HF) patients typically display various symptoms including peripheral congestion, low exercise tolerance, fatigue and dyspnea, which contribute to a progressive worsening of quality of life (QoL). Additionally, sexual activity remains an essential aspect of QoL, since, contrary to common belief, seriously ill patients mostly do not lose their interest in intimacy (Alberti et al., 2013). The American Heart Association asserts that sexual activity is appropriate and safe for patients with compensated and/or mild HF (NYHA I/II) (Levine et al., 2012) but unfortunately, an estimated 70% of male HF patients experience erectile dysfunction (ED) (Alberti et al., 2013). ED describes the persistent inability to achieve and/or maintain a penile erection sufficient for satisfactory sexual performance (Lue, 2000).

ED and HF share common risk factors including age, atherosclerosis, hyperlipidemia, hypertension, diabetes mellitus, smoking, obesity and sedentary lifestyle (Rastogi et al., 2005). Decreasing left ventricular function is associated with significantly reduced erectile function in cardiovascular high-risk patients and ED was shown to precede cardiovascular events in these patients (Baumhakel and Bohm, 2007). In addition, common underlying pathophysiological mechanisms such as atherosclerosis causing reduced blood-flow, arterial insufficiency and endothelial dysfunction are anticipated to contribute to both ED and HF progression (Rastogi et al., 2005). Furthermore, ED is also influenced by depression, exercise tolerance impairment, anabolic deficiency and pharmacological treatment (Alberti et al., 2013).

Several physiological pathways contribute to developing an erection. Contracted penile smooth muscle cells (SMC) in cavernosal arterioles and sinuses have to be transferred into the relaxed state in order to facilitate vasodilation and blood influx into the corpora cavernosa. With the increased intracorporal pressure, the surrounding fibrous tunica albuginea is stretched and thus compresses the subtunical venules. Thereby, the venous outflow is tremendously reduced contributing to initiation and maintenance of an erection (Fraga-Silva et al., 2013).

Sexual stimulation triggers nitric oxide (NO) release from penile nerves and activates the soluble guanyl cyclase (GC) in penile SMC to catalyze the conversion of GTP to cGMP. This results in the relaxation of SMCs and an increased blood flow into penile tissue.

Besides this well-known mechanism, the particulate guanyl cyclase (pGC), a cytoplasmic membrane-bound GC, additionally plays a pivotal role in erectile tissue. pGC is activated by binding of the C-type natriuretic peptide (CNP) to its receptor NPR-B. Subsequently, active pGC converts GTP to cGMP in penile SMCs (Kuthe et al., 2003). Additionally, CNP acts as an endothelium-derived hyperpolarizing factor (EDHF) and binding to its other receptor NPR-C elicits an activation of the inward rectifier K+ channel mediating the hyperpolarization and relaxation of penile SMCs (Kun et al., 2008). Thus, CNP essentially contributes to maintaining SMCs dilated and the penile tissue erect. ED patients display significantly lower NT-proCNP levels, which correlates with the erectile function assessed using the International index of erectile function (IIEF-5) (Vlachopoulos et al., 2010).

Furthermore, the RAAS system has been identified to play a paracrine role in penile tissue and interestingly, the physiological amount of angiotensin II produced in erectile tissues exceeds that found in the systemic plasma (Fraga-Silva et al., 2013). Angiotensin II elicits penile SMC

contraction by binding to its AT1 receptor. Consequently, angiotensin II contributes to the detumescence of the penis and termination of an erection. A hyperactivity of this peptide is known to augment the pathogenesis of ED (Becker et al., 2001).

Sacubitril/valsartan is a first-in-class angiotensin receptor-neprilysin inhibitor (ARNI), which both blocks the RAAS and augments natriuretic peptides, and was developed for the treatment of chronic HF. The clinical efficacy of sacubitril/valsartan in HF with reduced ejection fraction (HFrEF) patients has been demonstrated in the PARADIGM-HF study (McMurray et al., 2014). Sacubitril/valsartan not only established a significant benefit over enalapril in reducing cardiovascular death and hospitalizations due to HF as well as all-cause mortality, it also improved both health-related QoL, measured by Kansas City Cardiomyopathy Questionnaire (KCCQ) and EQ-5D, as well as symptom burden measured by NYHA class (Packer et al., 2015, McMurray et al., 2014). Furthermore, a post-hoc analysis of KCCQ demonstrated that patients treated with sacubitril/valsartan significantly improved nearly all criteria at the physical limitation and social limitation section when compared with enalapril, with the most significant changes in intimate/sexual relationships after 8 months of double-blind treatment persisting throughout 36 months (Chandra et al., 2018).

Based on these beneficial effects and the potential positive influence of enhanced CNP levels in erectile tissue, we hypothesize that sacubitril/valsartan may also enhance erectile function in male HFrEF patients, thereby contributing to improvement of QoL. Enhancement in erectile function will be evaluated using the renowned International Index of Erectile Function (IIEF), which was developed and validated in the 1990s and used in various clinical trials (Rosen et al., 1997, Wiltink et al., 2003). Since the questionnaire was developed for heterosexual men with the assumption of vaginal sex, homosexuals unfortunately cannot be included in this trial. [redacted]

1.2 Purpose

The purpose of this study is to evaluate the effect of sacubitril/valsartan in improving erectile function in male patients with chronic heart failure (NYHA II) and reduced ejection fraction (HFrEF) and erectile dysfunction (ED). Data from this study are intended to provide a thorough understanding of the impact of sacubitril/valsartan on male sexual function and therefore quality of life.

2 Study objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate the superiority of sacubitril/valsartan compared to enalapril regarding improvement in erectile function and ability in male patients with chronic heart failure and erectile dysfunction using the questionnaire International Index of Erectile Function (IIEF-15) at the end of the study	• Erectile function score at 3 months
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the early-onset effect as well as the effect at the end of the study of sacubitril/valsartan versus enalapril regarding improvement in sexual activity assessed using patient's self-reported frequency of sexual activity per month	• Self-reported frequency of sexual activity per month at months 1 and 3
• To assess the early-onset effect as well as the effect at the end of the study of sacubitril/valsartan versus enalapril regarding NT-proBNP levels	• NT-proBNP levels at months 1 and 3

3 Investigational plan

3.1 Study design

This is a randomized, double-blind, double-dummy, multi-center, active-controlled, interventional study to compare sacubitril/valsartan 97 mg/103 mg bid to enalapril 10 mg bid in improving erectile function in male patients with chronic heart failure (NYHA II) and reduced ejection fraction (HFrEF) and erectile dysfunction (ED).

The study comprises five obligatory and one optional visit over a period of approximately 14 weeks. Once patients' eligibility has been ascertained at Visit 1 (Screening), patients will be randomized at Visit 2 (Randomization) to receive either sacubitril/valsartan or enalapril in a 1:1 allocation during the double-blind period. At Visit 2, all efficacy assessments will be collected and used as baseline values. Double-blind treatment will be initiated with 5 mg bid enalapril or 49 mg/51 mg bid sacubitril/valsartan and up-titrated after 2 weeks to the final dose of 10mg bid enalapril or 97 mg/103 mg bid sacubitril/valsartan. According to the sacubitril/valsartan SmPC, initiation of treatment is recommended with the 24 mg/26 mg bid sacubitril/valsartan or 2.5 mg bid enalapril dose for certain patients. For these patients, an optional visit 4B after achieving the target dose of 97 mg /103 mg bid sacubitril/valsartan or 10 mg bid enalapril is mandatory. For allowed investigational treatment dose adjustments during double-blind period refer to **Section 5.5.4**.

All laboratory evaluations for planned visits and for unscheduled visits will be performed by the central laboratory. In order to have the results from the central laboratory available and enable a competent decision on randomization or up-titration at the respective visits, patients should come to the site approximately 3 to 4 days prior to the scheduled visit date for a blood draw (applies for Visit 2 (Randomization), Visit 3 and Visit 4 (Cave: Visit 4: safety lab only for patients who started with dose level 1)).

Further information on the visit schedule and data collection scheme can be found in**Table 6-1**.

Visit 1 (Screening)

At Visit 1 (-2 to -1 weeks) after signing informed consent, the inclusion and exclusion criteria will be checked for each patient to ascertain eligibility (see Section **4**). Among other criteria, they have been on a stable dose of enalapril of at least 10 mg/d, or equivalent ACEI or ARB for at least 4 weeks prior to visit 1 (see **Table 2-1**). A complete physical examination is required at Visit 1. Mild to moderate ED will be determined using a short form of the International Index of Erectile Function (IIEF-5). Screening potassium levels and eGFR as well as the biomarker NT-proBNP will be assessed by sending blood samples to the central laboratory and only patients with the required values per entry criteria will be eligible for entering the study. Detailed HF history and other relevant CV medical history will be recorded on eCRFs separately from other medical history.

The investigator may consider re-screening the patient at a later time if he/she believes that the patient's condition has changed and the patient may potentially be eligible. A minimum of 2

weeks must elapse between re-screenings and a patient may be re-screened once only (see **Section 6.1**).

Patients will continue stable intake of their current ACEI/ARB as well as concomitant medication until Visit 2 (Randomization). They should be reminded to come without taking their usual ACEI to Visit 2. For ACEI a **wash-out period of ≥ 36 hours** before first application of investigational treatment is mandatory.

Table 3-1 Minimum required pre-study daily doses of commonly prescribed ACEIs and ARBs

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

Visit 2 (Randomization)

At Visit 2 (timepoint 0), patients who meet all relevant entry criteria, including the required clinical laboratory values and safety criteria, will be randomized to one of the two treatment arms sacubitril/valsartan or enalapril bid, respectively. Patients should continue to take their background medication for heart failure during the study, with the exception of ACEI or ARBs which are replaced by the investigational treatment and must be discontinued before first application of the study drug (**washout period of ≥ 36 hours is mandatory for ACEI**). The first application of the study drug is planned for the day after Visit 2 (Randomization) – therefore, patients taking an ACEI should have discontinued their ACEI medical therapy in the evening before Visit 2 (e.g. if Visit 2 is scheduled for Wednesday the last ACEI medication should be taken by the patient on Tuesday evening. The patient will then start to take the first dose of double blind study medication (sacubitril/valsartan or enalapril) on Thursday morning). If the patient continued to take their usual ACEI, the start of study drug has to be postponed to assure a ≥ 36 hours washout before first application of the study drug.

Patients taking an ARB should discontinue their ARB medical therapy the day of Visit 2 (e.g. if Visit 2 is scheduled for Wednesday the last ARB medication should be taken on Wednesday. The patient will then start to take the first dose of double blind study medication (sacubitril/valsartan or enalapril) on Thursday morning).

Patients will start study treatment at dose level 2 (enalapril 5 mg bid or sacubitril/valsartan 49 mg/51 mg bid) unless the patients are suffering from moderate hepatic impairment, moderate renal impairment or patients with SBP ≥100 to 110 mmHg. These patients should be initiated at dose level 1, according to the the sacubitril/valsartan SmPC and the investigator's medical judgement (for these patients Visit 4B is neccessary). All patients must be stabilized on the chosen dose for 2 weeks.

At Visit 2, baseline IIEF-15, [redacted] and the sexual activity log need to be performed by the patients.

Visit 3 and 4

After 2 weeks of treatment (i.e. at Visit 3) the doses are up-titrated and after another 2 weeks (i.e. at Visit 4) all patients should have achieved the target dose of either 10 mg bid enalapril or 97 mg/103 mg bid sacubitril/valsartan, provided no safety and tolerability issues arise during up-titration. A blood draw for the safety lab needs to be performed 3-4 days prior to Visit 3 in order to have the results on the day of the visit to up-titrate the patient (for patients starting with dose level 1 an additonal safety lab is performed 3-4 days before Visit 4). The titration steps for the three dose levels are described in detail in **Section 5.5.3** (see **Table 5-1**). Every attempt should be made to keep the patients stable on dose level 3 in accordance with all safety parameters, which are symptomatic hypotension, renal dysfunction and/or hyperkalemia and should be handled according to the respective guidelines for management (see **Appendix 1**, **Appendix 2**, **Appendix 3**, **Appendix 4**, **Appendix 5** and **Appendix 6)**. In case of lab deviations an unscheduled visit may be scheduled at the discretion of the investigator to re-assess lab parameters and evaluate the efficacy of taken measures. Measurements showing an elevation of potassium levels above the predefined values should be repeated and confirmed in a non-hemolyzed sample before any action is taken (for a serum potassium concentration greater than or equal to 6.0 mmol/L please refer to **Appendix 4)** .

For the following visits (no up-titration), a blood draw for lab assessments has to be done during the visit.

At Visit 3 and Visit 4, IIEF-15, a physical examination and the current NYHA status is documented, as well as safety monitoring and adverse events. At Visit 4, the questionnaires IIEF-15 [redacted] will be applied as well as a blood draw for the biomarker NT-proBNP.

Visit 4B – Optional

For patients achieving target dose at Visit 4, Visit 4B is needed to evaluate safety criteria and ensure adequate medical management. Investigator's clinical judgement and discretion is advised. For patients who started with dose level 1, this visit is mandatory.

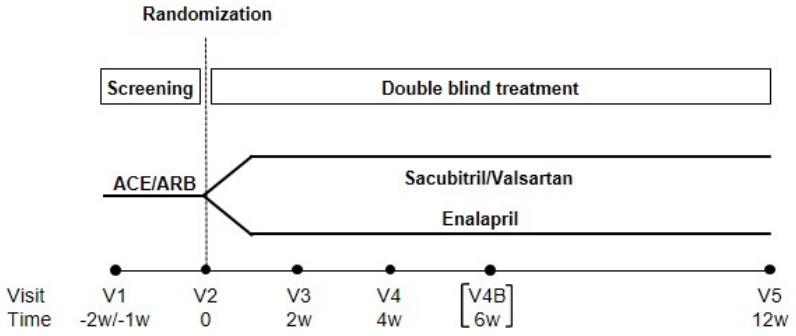
Visit 5 (End of Study)

After 3 months of treatment, a final assessment of patients is performed at Visit 5. IIEF-15 [redacted] questionnaires will be completed by patients at Visit 5. A blood draw for NT-proBNP assessment has to be done during the visit.

Unscheduled visits

In addition to the protocol-required visits, patients may be seen at any time throughout the study at the discretion of the investigator to follow any new lab abnormalities or AEs. All randomized patients, including any patient who has experienced a health event, should continue to receive double-blind treatment until the trial is completed, if possible in the opinion of the investigator. Unscheduled visits may also be performed throughout the study at the discretion of the investigator for up-titration of the study medication.

Figure 3-1 Study design



3.2 Rationale for study design

Sexual activity remains an essential aspect of QoL for patients with CHF. Unfortunately, erectile dysfunction is a common diagnosis in male patients with CHF constituting a substantial burden for the patients. Inhibition of neprilysin with sacubitrilat may enhance CNP levels in erectile tissue and contribute to maintaining an erection. It was already demonstrated that sacubitril/valsartan improved QoL in HFrEF patients including the intimate/sexual relationships section in a PARADIGM-HF post-hoc analysis (Chandra et al., 2018). Thus, the aim of the present study is to assess differences between sacubitril/valsartan versus enalapril in improving erectile function as assessed by the International Index of Erectile Function (IIEF-15) questionnaire in patients with HFrEF and ED. The questionnaire is established for assessing sexual function in ED patients and has been used in numerous clinical trials. For such a subjective endpoint as erectile function, a randomized, actively controlled, double-blind

interventional trial with a balanced study population is the state of the art and allows controlling the patients' treatment and thus reducing bias. Moreover, the study design is reasonable and adapted from recent studies for treatment of patients with CHF in terms of investigational treatment, duration of assessment period and the comparator. The study design is also in line with all required safety assessments and follow-ups for patients with CHF and for the treatment with sacubitril/valsartan and in compliance with the effective risk management plan for the product. Thus, events of angioedema, liver events, statin related events, and events of cognitive impairment are followed up by targeted questionnaires. Please refer to **Section 6.5** (safety assessments) for further details. Known risks of hypotension, renal impairment, and hyperkalemia are closely monitored to prevent severe events and are subject to separate guidance should such events occur. Please refer to **Sections 6.5.2** and **6.5.4** for assessments of blood pressure and laboratory assessments, respectively; and to **Appendix 1**, **Appendix 2**, **Appendix 3**, **Appendix 4** and **Appendix 5** for guidance to manage these risks.

Taken together, the present randomized, actively-controlled, double-blind, double-dummy approach is the most suitable design for achieving the study objective of demonstrating the superiority of sacubitril/valsartan versus enalapril in improving erectile function in patients with HFrEF and ED.

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

Strong clinical rationale for the target dose (97 mg/103 mg bid) as well as titration steps of sacubitril/valsartan is derived from the pivotal clinical trial PARADIGM-HF (McMurray et al., 2014) and this dosing schedule has been shown to be efficacious, safe (Senni et al., 2016) and is approved by the European Medicines Agency (EMA) for the treatment of symptomatic patients with chronic HF and reduced LVEF. The twice-daily dosing regimen of sacubitril/valsartan also ensures a sustained neprilysin (NEP) inhibition over 24 hours. The sacubitril/valsartan target dose of 97 mg/103 mg twice daily delivers a daily dose of valsartan equivalent to Diovan® 160 mg bid, the dose commonly recommended by current HF management guidelines (Ponikowski et al., 2016). With the purpose of this study to demonstrate the superiority of sacubitril/valsartan compared to enalapril in improving erectile function in patients with HFrEF and ED, we assume a measurable effect using the IIEF-15 questionnaire after 3 months of treatment.

3.4 Rationale for choice of comparator

Enalapril, the comparator chosen for this study, is an ACE inhibitor - the drug class considered first-line treatment by the current European therapy guidelines for the treatment of HFrEF patients (Ponikowski et al., 2016). ACE inhibitors and enalapril in particular, are the pharmacological standard of care for HFrEF management in Europe and – according to the current label – sacubitril/valsartan can be used to replace ACEI or ARBs in the management of HF. Since sacubitril/valsartan is tested in this study according to its label in treatment of patients with CHF, a standard-of-care comparator is thought to be most appropriate.
As a well-studied ACEI in HF, enalapril is used as the comparator in this study. Enalapril was studied in a number of previous large, outcome-driven studies, such as CONSENSUS (Group,

1987), SOLVD-Treatment (Investigators, 1991), and SOLVD-Prevention (Investigators et al., 1992).

Furthermore, in the pivotal clinical trial PARADIGM-HF (McMurray et al., 2014), enalapril was the active comparator for sacubitril/valsartan. Thus, enalapril was chosen as the active comparator for the present study. Enalapril will be used in this study according to its label and recommended dosing of 10 mg bid, which is the most commonly recommended target dose for HFrEF patients and has been shown to reduce the risk of death and hospitalizations in HF patients (Investigators et al., 1992).

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

Both sacubitril/valsartan and enalapril are approved in the indication investigated within this study. Please refer to the corresponding Summary of Product Characteristics (SmPC) of each product as well as the Investigator's Brochure (IB) for sacubitril/valsartan for known adverse reactions, or special precautions on both IMPs (provided to all participating sites).

Patients will be instructed not to take any renin angiotensin aldosterone system (RAAS) blocking agents (ACEIs or ARBs) before start of study treatment in order to avoid excess RAAS blockade. **For ACEI a ≥ 36h washout period is mandatory**. The risk of temporary discontinuation of concomitant ACEIs or ARBs will be minimal as it will be reflective of the typical dosing schedule of most ACEIs and ARBs.

All patients will be allowed to continue receiving their other background CV medications.

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

If there is any question that the patient will not reliably comply, the patient should not be entered in the study. Participating patients will benefit from careful monitoring and follow-up during the entire study duration.

4 Population

This is an outpatient multi-center clinical study to be conducted in Germany. The goal is to randomize 200 patients in about 40 centers. Since a 30% screening failure rate is expected, approximately 286 patients will be screened. The study population will consist of a representative group of adult (≥18 and ≤ 75) male HFrEF patients in NYHA class II with mild to moderate ED. Eligible patients should be on a stable dose of an ACEI or an ARB as well as bisoprolol/metoprolol for at least 4 weeks prior to entering into the study.

The investigator must ensure that all patients who meet the inclusion criteria and do not fulfill any of the exclusion criteria are offered enrollment in the study. No additional parameter can be applied by the investigator.

4.1 Inclusion criteria

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

1. Patients must give written informed consent before any assessment is performed and must be willing and capable to comply with all study procedures
2. Male Outpatients ≥ 18 and ≤ 75 years of age
3. Patients with a diagnosis of CHF NYHA class II and reduced ejection fraction (< 40%) (assessed by any local measurement using echocardiography, CT scanning, MRI or ventricular angiography ≤ 6 months prior to Visit 1)
4. Plasma NT-proBNP level of ≥ 300 pg/mL at Visit 1
5. Patients must be living in a stable and sexually active heterosexual partnership for at least 6 months prior to Visit 1
6. Patients must have a mild to moderate erectile dysfunction determined using the IIEF-5 questionnaire (> 7 and ≤ 21 IIEF units) at Visit 1 and Visit 2
7. No usage of any available drug for erectile dysfunction (e.g. sildenafil, tadalafil) for at least 2 weeks prior to Visit 1 and 4 weeks prior to Visit 2
8. Patients must be on an ACEI or an ARB at a stable dose for at least 2 weeks prior to Visit 1 and 4 weeks prior to Visit 2
9. Patients must be treated with a stable dose of bisoprolol/metoprolol, unless the use of β-blockers is contraindicated or not tolerated (reason should be documented) for at least 2 weeks prior to Visit 1 and 4 weeks prior to Visit 2 (β-blockers other than bisoprolol/metoprolol are not allowed per protocol)
10. Patients must be literate in German

4.2 Exclusion criteria

Patients/subjects fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients/subjects.

1. Use of other investigational drugs during the study and within 30 days or 5 half-lives, whichever is longer before enrolment and at enrolment
2. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes, ACEIs, ARBs or NEP inhibitors, as well as known or suspected contraindications to the study drugs
3. Previous history of intolerance to recommended target doses of ACEIs or ARBs
4. Known history of angioedema
5. Requirement of treatment with a dual RAAS blockade, e.g. a treatment with both, ACEIs and ARBs or concomitant treatment with aliskiren
6. Current acute decompensated HF (exacerbation of chronic HF manifested by signs and symptoms that may require intravenous therapy)
7. Symptomatic hypotension and/or a systolic blood pressure (SBP) ≤100 mm Hg at Visit 1 (Screening) or Visit 2 (Randomization)
8. Estimated glomerular filtration rate (eGFR) < 30mL/min/1.73m^2 at Visit 1 (Screening) or Visit 2 (Randomization) as calculated by MDRD formula
9. Serum potassium level > 5.2mmol/L at Visit 1 (Screening) or Visit 2 (Randomization)
10. Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid or other major CV surgery, percutaneous coronary intervention (PCI) or carotid angioplasty within the 3 months prior to Visit 1
11. Coronary or carotid artery disease likely to require surgical or percutaneous intervention within the 3 months after Visit 1
12. Implantation of a pacemaker, implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy pacemaker / defibrillator (CRT-P/D), or upgrade of an existing device or revision of device leads within 3 months prior Visit 1 or intent to implant such a device during the study
13. Heart transplant or ventricular assistance device (VAD) or intent to transplant (on transplant list) or implant a VAD
14. History of severe pulmonary disease including COPD (Patients with significant chronic obstructive pulmonary disease contributing to dyspnea or patients whose COPD medication has been altered within 2 weeks prior to Visit 1 and 4 weeks prior to Visit 2)
15. Diagnosis of chemotherapy induced cardiomyopathy within the 12 months prior to Visit 1
16. Documented untreated ventricular arrhythmia with syncopal episodes within the 3 months prior to Visit 1
17. Known symptomatic bradycardia or second or third degree heart block without a pacemaker
18. Known presence of hemodynamically significant mitral and/or aortic valve disease, except mitral regurgitation due to left ventricular dilatation

19. Presence of other hemodynamically significant obstructive lesions of left ventricular outflow tract, including aortic and sub-aortic stenosis
20. Known history of familial long QT syndrome or known family history of Torsades de Pointes
21. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs, including but not limited to any of the following:
    - AST or ALT values exceeding 2 x upper limit of normal (ULN)
    - History of active inflammatory bowel disease during the 12 months before Visit 1
    - Current duodenal or gastric ulcers during the 3 months prior to Visit 1
    - Gastric bypass
    - Evidence of severe hepatic impairment, biliary cirrhosis or cholestasis, classified as Child-Pugh C
    - History of hepatic encephalopathy, history of esophageal varices, history of portocaval shunt
    - Active treatment with bile sequestering agents such as cholestyramine or colestipol resins
22. Presence of any other disease with a life expectancy of < 1 years
23. Presence of known bilateral renal artery stenosis
24. Penile anatomical defects and Peyronie's disease
25. Foreseeable usage of any available drug for erectile dysfunction (e.g. sildenafil, tadalafil) during the study
26. Co-Medication with an influence on erectile function such as digoxin, anticholinergic anti-depressants, alpha blockers finasteride and calcium channel blockers
27. Recent (4 weeks prior to Visit 1) or planned (within the 14 weeks after Visit 1) change in statin or spironolactone therapy
28. Diabetes mellitus Type I or insulin-dependent Type II
29. Prostate-specific antigen (PSA) levels higher than 4 ng/mL at Visit 1 or known prostate cancer
30. Spinal cord injury, ileostomy, prior surgery or radio therapy for rectal or prostate cancer and radical prostatectomy
31. Presence of peripheral artery occlusive disease and/or stenosis of the common and internal iliac artery
32. Patients with ongoing alcohol and/or drug abuse and/or severe depression (defined as patients with altered medication or hospitalization within 4 weeks prior to Visit 1 and Visit 2)
33. Presence of any neurodegenerative disease or polyneuropathy
34. Hormonal abnormalities such as hypogonadism, hyperprolactinemia, hyper- and hypocortisolism and medically untreated hyper- and hypothyroidism
35. Obesity based on a body mass index $\geq$35 kg/m^2, frail patients or patients with cardiac cachexia or a body mass index <18.5 kg/m^2

36. Any surgical or medical condition, which in the opinion of the investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Double blind treatment

All eligible patients will be randomized in a 1:1 allocation to receive either sacubitril/valsartan or enalapril in addition to optimal CHF therapy, as considered appropriate by the investigator and in accordance with standard therapy guidelines, but with the exception of an ACEI or ARB, as this will be replaced by investigational treatment at Visit 2 (Randomization). The use of an ACEI or an ARB in addition to investigational treatment is **strictly prohibited.** For ACEIs a washout period of ≥ 36 hour is mandatory. During the dosing of study medication, i.e. beyond randomization until the end of the study, the intake of ACEIs or ARBs remains prohibited (in case of treatment interruption/discontinuation see **Section 5.5.5** and **Section 5.5.6**).

The following study drugs will be provided:

- Sacubitril/valsartan 24 mg/26 mg film-coated tablets (sacubitril/valsartan dose level 1)
- Placebo to match sacubitril/valsartan 24 mg/26 mg film-coated tablets (placebo matching sacubitril/valsartan dose level 1)
- Sacubitril/valsartan 49 mg/51 mg bid film-coated tablets (sacubitril/valsartan dose level 2)
- Placebo to match sacubitril/valsartan 49 mg/51 mg bid film-coated tablets (placebo matching sacubitril/valsartan dose level 2)
- Sacubitril/valsartan 97 mg/103 mg film-coated tablets (sacubitril/valsartan dose level 3)
- Placebo to match sacubitril/valsartan 97 mg/103 mg film-coated tablets (placebo matching sacubitril/valsartan dose level 3)
- Enalapril 2.5 mg film-coated tablets (enalapril dose level 1)
- Placebo to match enalapril 2.5 mg tablets (placebo matching enalapril dose level 1)
- Enalapril 5 mg film-coated tablets (enalapril dose level 2)
- Placebo to match enalapril 5 mg tablets (placebo matching enalapril dose level 2)
- Enalapril 10 mg film-coated tablets (enalapril dose level 3)
- Placebo to match enalapril 10 mg tablets (placebo matching enalapril dose level 3)

Target doses: Sacubitril/valsartan 97 mg/103 mg bid and enalapril 10 mg bid

All tablets have different shapes and colors. Therefore, the study will be designed as a double-blind, double-dummy trial to ensure the blinding during the entire course of the study. To

maintain the blinding, patients will be required to take their assigned active treatment tablet along with placebo matching the opposite treatment twice daily (morning and evening dose) in addition to their conventional concomitant therapy.

Sacubitril/valsartan and its matching placebo will be provided in HDPE bottles and/or blister packs. Enalapril and its matching placebo will be provided in HDPE bottles and/or blister packs.

5.1.2 Additional treatment

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

5.2 Treatment arms

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

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

5.3 Treatment assignment and randomization

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

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

The randomization scheme for patients/subjects will be reviewed and approved by a member or delegate of the Randomization Group.

5.4 Treatment blinding

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

Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions:

- Specific vendors whose role in the trial conduct requires unblinding (e.g. IRT)

- Drug supply management

A double-dummy design is used because the identity of the study drug cannot be disguised, as the drug products are visibly different.

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

5.5 Treating the patient

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

5.5.1 Patient numbering

Each patient is uniquely identified by a Patient-ID Number assigned by Novartis. The Patient-ID Number is composed of a site number and a sequential number. Once assigned to a patient, the Patient-ID Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number available in the electronic data capture (EDC) system. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the CRF book with a matching Subject Number in the EDC system to enter data.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the appropriate Screening period CRF.

5.5.2 Dispensing the study drug

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

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the 2 treatment arms and a specific dose. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

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

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

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

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

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

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

Patients will be provided with medication packs containing the study drug corresponding to their assigned treatment arm and dose level, sufficient to last until their next scheduled visit. In order to maintain blinding, patients will be required to take two tablets (one sacubitril/valsartan or its matching placebo and one enalapril or its matching placebo) twice a day for the duration of the study. **Table 5.1** summarizes the study drug that will be taken during the double-blind period.

Patients will begin treatment with dose level 2 for 2 weeks. At Visit 3, patients will be up-titrated to dose level 3 unless safety monitoring criteria prevent up-titration. According to the sacubitril/valsartan SmPC and the investigator's medical judgement, patients suffering from moderate hepatic impairment (Child Pugh B), moderate renal impairment or patients with SBP ≥100 to 110 mmHg should be initiated at dose level 1. They will be up-titrated every 2 weeks (unless safety monitoring criteria prevent up-titration) until they reach dose level 3. Visit 4B is a mandatory visit for patients achieving target dose (dose level 3) at visit 4 to evaluate safety criteria and ensure adequate medical management.

Table 5-1 Study drug dispensed during the double-blind period

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

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

Patients will be instructed to take their morning study drug doses at approximately 08:00 (8 AM) and their evening study drug doses at approximately 19:00 (7 PM). The study medications should be taken with a glass of water with or without food. If the patient misses taking any study drug dose, he should take it as soon as possible, unless if it is almost time for the following scheduled dose. In this case, the patient should skip the missed dose and return back to his regular study drug administration schedule.

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

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

5.5.5 Permitted dose adjustments and interruptions of study treatment

For patients who are unable to tolerate the protocol-specified dosing scheme, dose adjustments and interruptions of investigational drug are permitted in order to keep the patient on study drug. The following guidelines must be followed:

Once patients achieve the target study drug dose, every attempt should be made to maintain the target study drug dose level (dose level 3) for as long as possible throughout the trial. If, however, in the opinion of the investigator, the patient does not tolerate the target dose of the study drug, the investigator should consider whether non-disease modifying medication (e.g. diuretics, nitrates) can be reduced to rectify the situation, before considering to reduce the dose of study drug to the next lower dose level. In addition, the investigator may adjust the doses of disease -modifying medications, if he/she believes that they are more likely causes of adverse events. If such adjustments of concomitant medications are not medically indicated, the investigator may down-titrate the dose of study drug to the next lower dose level up to a complete withdrawal of the investigational treatment, if necessary. In such cases, the patient should be re-challenged with the higher dose when the investigator feels that doing so is appropriate; the re-challenge should be performed according to the guidance provided in this section (see below) of the protocol.

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

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

- Hyperkalemia (see **Appendix 4**)
- Symptomatic hypotension (see **Appendix 5**)
- Clinically significant decrease in eGFR or clinically significant increase in serum Creatinine (see **Appendix 6**)
- Worsening hepatic function (see **Appendix 2**)

After randomization, temporary study drug discontinuation for any reason does not automatically constitute withdrawal from the study and should not lead to the patient being withdrawn from the study.

Adjustment of study drug dose level

If despite adjustment of concomitant medications per the guidance provided above the situation is not rectified, the investigator may consider adjusting the study medication according the following instructions.

During the double-blind treatment period down-titration of the study drug at any time will be allowed based on the safety and tolerability criteria defined in **Appendix 1**, **Appendix 2**, **Appendix 3**, and **Appendix 4**. If down-titration is necessary, the patient should be down titrated to the next dose level (see **Table 5-1**). The patient may continue receiving the lower dose level for a recommended period of 1 to 2 weeks before re-challenging the patient with the next higher dose level. For example, a patient who encounters tolerability problems at the target dose level (dose level 3), should receive the study drug at dose level 2 for 1 to 2 weeks. Then, he should be re-challenged with up-titration back to dose level 3.

If the tolerability issues are not alleviated, the investigator may lower the study drug dose further to the next lower level for 1 to 2 weeks, up to temporary withdrawal of the study drug. Again, once stable, the patient should be re-challenged with up-titration to the next higher dose level every 1 to 2 weeks in an attempt to bring back the patient gradually to the target study drug dose level (dose level 3). The investigator may choose the next dose level for down- or up-titration according to his or her judgment **(Table 5-1)**.

In some cases, according to the safety and tolerability criteria and the investigator's judgment, dose level 1 or 2 could be maintained if he/she considers that the patient's condition would not allow an up-titration to the target dose of study medication (level 3). In this case, it would be acceptable to maintain the patient at dose level 2 (or lower), to assure treatment with the highest dose level tolerated by the patient.

Study drug restart after temporary treatment interruption

Study drug should be reintroduced after 1-2 weeks in those who temporarily discontinue as soon as medically justified in the opinion of the investigator.

Once the investigator considers the patient's condition appropriate for receiving the study drug, the investigator should re-start the patient on the study drug at the most appropriate and allowable dose level **(Table 5-1)** per his/her medical judgment. If tolerated based on the safety

and tolerability criteria in **Appendix 1**, **Appendix 2**, **Appendix 3**, and **Appendix 4** the patient should be up-titrated to the next dose level (up to dose level 3) every 1 to 2 weeks, as per the investigator's judgment.
Patients re-started on the study drug will retain their original randomization and study identification numbers. Should the patient not tolerate the re-start study drug dose level, he may be down-titrated again (if appropriate) or discontinue the study medication. Up-titration or reintroducing the study drug could be considered by the investigator as soon as medically justified in his/her medical judgment.
Study visits should occur as close as possible to the time points indicated in **Table 6-1**. The timeframe between the regular visits should be maintained as scheduled, irrespective of the number of unscheduled visits that may be performed in between, according to the visit and time schedule described in **Table 6-1**.

Any changes in the study drug dose level, including temporary/permanent withdrawal or re-start of the study drug, must be recorded on the Dosage Administration Record CRF.

5.5.6 Rescue medication

Guidance on handling hyperkalemia, hypotension and renal dysfunction are provided in **Appendix 1**, **Appendix 4**, **Appendix 5** and **Appendix 6**. If necessary, patients may receive open-label ACEI and/or ARBs **ONLY** if study medication is interrupted temporarily or discontinued permanently. NOTE that a washout phase of ≥ 36 hours is required for the study drug (in case the patient is switched to an ACEI), but also for any ACEI before (re-)introducing study drug.

Use of rescue medication must be recorded on the appropriate CRF.

5.5.7 Concomitant medication

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

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

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

ACEIs and ARBS

The patients' pre-study ACEIs or ARBs will be replaced by the study drug. As per inclusion criteria, the patients need to be on stable HF therapy regimen for at least 4 weeks prior to Visit 2 and should remain on a stable regimen, if medically justified, throughout the entire study duration.

The concomitant use of open-label ACEIs or ARBs is strictly prohibited while the patient is receiving study medication. If the investigator believes that addition of an ACEI or ARB is necessary, then study drug must be discontinued. Study medication should be stopped ≥ 36 hours prior to addition of **open-label ACEI**. If not already treated with an aldosterone antagonist, consideration should be given to adding this therapy rather than an ACEI or ARB.

Similarly, if study medication is to be restarted, the open-label **ACEI should be discontinued ≥ 36 hours prior to resuming study medication**.

Phosphodiesterase-5 (PDE-5) inhibitors

The use of Phoshodiesterase-5 inhibitors (e.g. sildenafil, vardenafil, tadalafil and compounds with similar characteristics) **is not allowed during the study**.

However, there is a risk that patients make use of PDE5i, despite being not allowed by the study protocol. For this reason, investigators are advised to make all efforts to make the patient aware that use of PDE5i is not allowed. The investigator should educate the patient concerning the increased possibility of the occurrence of hypotension.

Statins

Caution should be exercised upon co-administration of statins such as atorvastatin, simvastatin, pravastatin and/or pitavastatin and study medication, due to potential interactions between statins and sacubitril/valsartan.

Other drugs with a potential impact on erectile function

The treatment with the following medications with a potential influence on erectile function are not allowed:

- **Digitoxin, Digoxin** (e.g. Digacin, Lanicor, Lenoxin and compounds with similar characteristics)
- **Calcium channel blockers** (e.g. Verapamil, Gallopamil, Diltiazem, Amlodipin, Nitrendipin, Felodipin, Nidedipin and compounds with similar characteristics)
- **Alpha blockers** (e.g. Alfuzosin, Tamsulosin, Doxazosin, Phentolamin, Prazosin, Uradipil, Ergotamin and compounds with similar characteristics)
- **Anticholinergic anti-depressants** (e.g. amitriptyline, doxepin and compounds with similar characteristics)
- **Finasteride**

Potential interactions between sacubitril/valsartan and lithium or non-steroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase-2 (COX-2) inhibitors should be considered.

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

Medications known to raise potassium levels

Potassium-sparing diuretics, potassium supplements, aldosterone antagonists, and any other medications known to raise potassium levels should be used with caution while the patient is receiving the study medication due to the increased possibility of occurrence of hyperkalemia. The investigator is encouraged to assess patients' potassium levels regularly, especially in those who are receiving these medications. Guidelines for the management of hyperkalemia can be found in **Appendix 4**.

5.5.8 Prohibited medication

Use of the treatments displayed in the **Table 5-2** is NOT allowed after the start of the investigational drug. For ACEI a washout period of ≥ 36 hours is mandatory.

In order to avoid excessive RAAS inhibition, it is crucial to respect the washout period and instruct the patient to not take any ACEI or ARB while taking double-blind study medication.

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

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

β-blockers other than bisoprolol/metoprolol are not allowed per protocol due to interference with erectile function.

Table 5-2 Prohibited medication

Medication	Prohibition period	Action taken
Any ACEI, ARB or Renin inhibitors	Double blind period (≥ 36h washout period for ACEI)	Prohibited until at least 36 hours after study drug discontinuation/interruption/end of study (for ACEI). In case these drugs are taken / need to be taken during the double-blind treatment period of the study, discontinue study drug
PDE5i	Double blind period	Discontinue before randomization, proh bited throughout the study. No action required with study medication
Bile acid sequestering agents (e.g. Cholestyramine, Colestipol)	Double blind period	Discontinue before randomization, prohibited throughout the study. No action required with study medication
Calcium channel blockers (e.g. Verapamil, Amlodipin)	Double blind period	Discontinue before randomization, prohibited throughout the study. No action required with study medication
Alpha blockers (e.g. Tamsulozin, Prazosin, Ergotamin)	Double blind period	Discontinue before randomization, prohibited throughout the study. No action required with study medication
Anticholinergic anti-depressants (e.g. Amitryptiline, Doxepin)	Double blind period	Discontinue before randomization, prohibited throughout the study. No action required with study medication
Digitoxin	Double blind period	Discontinue before randomization, prohibited throughout the study. No action required with study medication
Digoxin (e.g. Digacin, Lanicor)	Double blind period	Discontinue before randomization, prohibited throughout the study. No action required with study medication
β-blockers other than bisoprolol/metoprolol	Double blind period	Prohibited throughout the study. No action required with study medication
Finasteride	Double blind period	Discontinue before randomization, prohibited throughout the study. No action required with study medication

5.5.9 Emergency breaking of assigned treatment code

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

patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

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

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

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

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

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

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

For all patients/subjects a safety follow-up visit should be conducted (e.g. by telephone) 30 days after last visit (Visit 5) or PD, or TSD. The information to be collected at this follow up visit includes concomitant medications, adverse events, and survival status.

5.6.2 Discontinuation of study treatment

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

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

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Any situation in which study participation might result in a safety risk to the patient
- Suspected occurrence of angioedema. A patient with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the investigator and constitute a reason for temporary or permanent discontinuation of study treatment
- Use of prohibited treatment as per **Table 5-2**. In case of initiation of open-label ACEI during the double blind treatment period, study medication must be stopped for ≥36 hours prior to initiation of open-label ACEI. The open label ACEI must be stopped for ≥36 hours prior to re-initiation of study drug
- Depending on the serum potassium, blood pressure, or eGFR, patients may need to have their study drug dose or the dose of another concomitant medication reduced or discontinued, or, if appropriate, have potentially contributing agents adjusted. Please refer

to **Appendix 4**, **Appendix 5**, and **Appendix 6** for treatment guidelines for hyperkalemia, hypotension, or renal dysfunction, respectively.

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study. The patient should return to the clinic as soon as possible, after discontinuation of study drug, for a study treatment discontinuation visit. Treatment discontinuation visit assessments detailed in the "unplanned treatment discontinuation visit" in **Table 6-1** should be completed and recorded in the eCRF. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the appropriate CRF.

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

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

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

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

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

5.6.3 Withdrawal of informed consent

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

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

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

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

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

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

5.6.4 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his planned end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason specified in the clinical trial study contract. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely discontinued patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The sponsor will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

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

Patients/subjects must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

Table 6-1 Assessment schedule

Visit	**1**	**2**	**3**	**4**	**4B**	**5**	**TD and/or PSD**	
Time	**-2w to -1w**	**0**	**2w**	**4w**	**6w**	**12w**		
Obtain informed consent	X							
Inclusion/Exclusion criteria	X	X						Some exclusion criteria apply for both Visit 1 and Visit 2
Demography	X							
Medical History	X	X[1]						
NYHA Classification	X	X	X	X	(X)	X	X	
Previous and concomitant drug/non-drug treatments	X	X	X	X	(X)	X	X	
Physical Exam	X	X	S	S	(S)	X	S	At Visit 1 (Screening), 2 (Randomization), and 5 (EOS) a full physical exam is performed; at all other visits a short exam is to be performed (see Section 6.5.1)
Height	X							
Weight	X					X	X	
Vital signs	X					X	X	
IIEF-15		X	X	X		X	X	
IIEF-5	X	X						
Dispense Sexual Activity Log		X						
Sexual Activity Log		X	X[4]	X[4]	X[4]	X[4]	X	Sexual activity Log is completed by the patient once a week. Baseline value is assessed at Visit 2
[redacted]								
Diagnostic and Laboratory evaluations	X[2]	X[3]		X		X	X	Hematology and Biochemistry
NT-proBNP	X	X[3]		X		X	X	
Laboratory assessment			X[3]	(X[3,5])	(X)			Abbreviated assessment for Potassium, AST and ALT and Creatinine/eGFR.
Dispense Study Medication		X	X	X				

Visit	**1**	**2**	**3**	**4**	**4B**	**5**	**TD and/or PSD**	
Time	**-2w to -1w**	**0**	**2w**	**4w**	**6w**	**12w**		
Drug accountability			X	X	(X)	X	X	
Adverse event monitoring	X	X	X	X	(X)	X	X	
Contact IVRS/IWRS	S	S	S	S	(S)	S	S	
Study Completion form							X	

TD = Study treatment discontinuation; PSD = Premature subject/patient discontinuation
X = assessment to be recorded on clinical data base
S = assessment to be recorded on source documentation only
"( )" = Assessments for Visit 4B are in brackets, as Visit 4B is a visit not applying to all patients
IIEF = International Index of Erectile Function

[redacted]

[1] = Medical history as far as needed for inclusion and exclusion criteria
[2] = PSA level will be determined at Visit 1
[3] = Blood draw 3-4 days before Study Visit (central lab)
[4] = sexual activity log is completed once a week by the patient
[5] = The laboratory assessment (safety lab) only applies for patients who started with dose level 1 (Cave: these patients need to come 3-4 days before Visit 4 for the blood draw). The Diagnostic and Laboratory Evaluations at Visit 4 are performed at the regular visit.

6.1 Information to be collected on screening failures

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

Re-screening

If a patient is not eligible to enter the double-blind treatment epoch (i.e. screening failures), the investigator may consider re-screening the patient at a later time, if he/she believes that the patient's condition has changed and the patient may be potentially eligible. However, rescreening will only be possible for inclusion criteria 4, 6, 7, 8 and 9 and exclusion criteria 1, 7, 8, 9, 14, 25, 26 and 27. In this case, a completely new patient number will be allocated to the patient and all Visit 1 assessments will be performed again. A patient may be re-screened once only.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: year of birth, age, sex, race, source of patient referral (if applicable), the patients' living conditions, smoking status, relevant medical history/current medical condition present before signing informed consent (where possible, diagnoses and not symptoms will be recorded) previous drug/non-drug therapy of HF (prior Visit 1 and 2), concomitant medication and non-drug therapy. Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.3 Treatment exposure and compliance

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.4 Efficacy

- IIEF-15 questionnaire
- Patient-reported frequency of sexual activity
- NT-proBNP
- [redacted]

6.4.1 IIEF-15 questionnaire

The International Index of Erectile Function (IIEF-15) is a patient self-reported questionnaire to assess ED in male patients (see annex for detailed information). It consists of 15 questions assessing five main principles associated with ED: erectile function, orgasmic function, sexual

desire, intercourse satisfaction and overall satisfaction. For each question, 0-5 points can be achieved with 5 being the best outcome (Rosen et al., 1997). In this study, the IIEF-15 will be completed by patients at baseline (Visit 2), as well as at 2 weeks (Visit 3), at 1 month (Visit 4) and at 3 months (Visit 5) and all categories will be evaluated separately: erectile function (questions 1-5; 15), orgasmic function (questions 9-10), sexual desire (questions 11-12), intercourse satisfaction (questions 6-8) and overall satisfaction (questions 13-14).

6.4.2 Patient-reported frequency of sexual activity

Since the quantitative amount of sexual activity is not covered in the IIEF-15, patients will keep a diary to log any sexual activity during the whole study period starting with an initial assessment at Visit 2 covering sexual activity the week before Visit 2. This self-assessment will be completed by the patients on an electronic device (tablet). Patients are asked to complete the diary once per week until end of the study (Visit 5). The diary consists of seven items assessing the patients' sexual activity of the previous 7 days.

6.4.3 NT-proBNP

Plasma NT-proBNP will be obtained in all patients by using the central laboratory at Visit 1 to determine eligibility for participation in the trial. In addition, plasma NT-proBNP is assessed at Visit 2, 4 and 5.

[redacted]

6.4.5 Appropriateness of efficacy assessments

IIEF-15

The International Index of Erectile Function Questionnaire (IEF-15) is a validated, multi-dimensional, self-administered 15-item questionnaire for the assessment of erectile function. The IIEF was developed and validated in the 1990s and used in various clinical trials (Rosen et al., 1997, Wiltink et al., 2003).

Therefore, the IIEF-15 is an appropriate tool to measure erectile function in clinical trials.

[redacted]

Patient-reported sexual activity

Although the IIEF-15 questionnaire is assessing erectile function, it is not measuring sexual activity other than intercourse with vaginal penetration, or the attempt to vaginal intercourse. However, sexual activity can also include sexual actions like masturbation, sexual foreplay or intimacy with a partner. Sexual activity other than intercourse is also an important part of Quality of Life (McCabe, 1997). Therefore, a sexual activity diary was developed to assess the patients' sexual activity and QoL associated with the patients'sexual activity.

NT-proBNP

NT-proBNP is a biomarker relevant to the pathophysiology of cardiovascular disease and has shown prognostic value in large clinical trials. Therefore, NT-proBNP is an appropriate readout for the progression of cHF (Zile et al., 2016, McMurray et al., 2014).

6.5 Safety

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

6.5.1 Physical examination

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

A short physical exam will include the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). A short physical exam will be at all visits starting from Visit 3 except where a complete physical examination is required (see above).

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the CRF capturing Medical History. Significant findings made after first administration of investigational drug which meet the definition of an Adverse Event must be recorded on the appropriate CRF capturing AEs.

6.5.2 Vital signs

Vital signs include BP and pulse measurements. BP will be measured by using a standard sphygmomanometer with an appropriate size cuff and the non-dominant arm in the sitting position after 5 minutes of rest.

Guidelines for the management of BP are provided in **Appendix 5**.

6.5.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at all visits, until the EOS visit.

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in **Appendix 1**.
The investigator or his/her designee should review the central laboratory results as soon as they become available to decide on whether any adjustments in the patient's study drug or non-study drug regimen are needed. Therefore, unscheduled visits are possible based on investigator's discretion.

All central laboratory results will be communicated to the investigators and the sponsor. Details on the collection, shipment of samples and reporting of results by the central laboratory will be provided to investigators in the laboratory manual.

Laboratory values that exceed the boundaries of a notable laboratory abnormality must be commented on by the investigator in the Comments screen of the patient's eCRF and additional laboratory evaluations should be performed, as judged appropriate by the investigator. If the laboratory abnormality induces clinical signs or symptoms, or requires therapeutic intervention, then the diagnosis or medical condition must be entered on the AEs screen of the patient's eCRF. If the laboratory abnormality is the primary reason for an unforeseen hospitalization or otherwise fulfills the seriousness category of an AE, then the procedure for rapid notification of SAEs must be followed. Likewise, if the laboratory abnormality leads to discontinuation from the study drug (temporarily or permanently), the patient must be followed until the abnormality resolves or until it is judged to be permanent.

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential counts, and platelet count will be measured at Visits 1, 2, 4, 5 and in case of study treatment discontinuation (TD) or premature subject/patient discontinuation (PSD).

6.5.4.2 Clinical chemistry

Glucose, blood urea nitrogen (BUN), Blood urea, creatinine, creatinine kinase, total bilirubin, AST, ALT, alkaline phosphatase, INR, GFR, HbA1c absolute, HbA1c relative, sodium, potassium, chloride, calcium, total protein, albumin, HDL, LDL, triglycerides, and uric acid will be measured at visits 1, 2, 4, 5 and in case of TD or PSD.

BUN, creatinine, GFR, potassium and urea will be obtained from patients at every visit when a complete laboratory test is not done (i.e., Visit 3, 4 and 4B, please see **Table 6-1** for details).

The latter is true for all unscheduled visits done with up-titration intention.

6.5.4.3 Urine analysis

Not applicable

6.5.5 Electrocardiogram (ECG)

Not applicable.

6.5.6 Pregnancy and assessments of fertility

Not applicable.

6.5.7 Angioedema

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

It is important that the investigator pays special attention to any swelling or edema that may resemble angioedema or angioedema-like events that may be reported by patients. If such an event occurs, the investigator will complete an Adjudication Questionnaire for an Angioedema-like Event form (provided by Novartis) to summarize the event, its treatment, and its ultimate outcome. This report along with the requisite medical documentation must be submitted to Novartis as soon as possible. Follow-up reports must be communicated to Novartis as soon as new information regarding the event becomes available. All hospital records related to the event must be communicated to Novartis. The investigator may be also be contacted by Novartis regarding AEs that may resemble an angioedema-like event. A list of terms that are considered "angioedema-like" (e.g., periorbital swelling) will be provided to sites in a manual. The investigator or his/her delegated staff must complete the required forms and provide the required medical records for all such events, regardless of whether the investigator views the event in question as angioedema or not.

All angioedema reports will be forwarded to an Angioedema Adjudication Committee by Novartis for assessment. Information regarding this committee is outlined in Section 8.5. Details on the procedures for reporting angioedema events will be provided to investigators in a manual.

6.5.8 Cognitive Impairment

Angiotensin receptor blockade has been suggested to improve cognitive function, as might overall improvement in cardiac and vascular function. Thus, improvements in cardiac function and cerebral blood flow by LCZ696 are hypothesized to potentially improve vascular effects and, thereby, cognition. However, neprilysin is one of multiple enzymes involved in the breakdown of amyloid β, a peptide linked to cognitive impairment. Thus, cognitive function resulting from combined angiotensin receptor blockade and neprilysin inhibition with LCZ696 is subject to standardized follow-up.

It is important that the investigator pays attention to any events of cognitive impairment or related events that may be reported by patients. If such an event occurs that meets criteria for

serious adverse event, the investigator will complete a separate questionnaire for a Dementia-related Event form (provided by Novartis) to summarize the event, its further diagnostic tests performed, and its related information. A list of terms that are considered "dementia-like" (e.g., presenile dementia, memory impairment) will be provided to sites in a manual.

6.5.9 Statin-related Events

Statin-related events are subject to additional safety assessments and thus are followed with a standardized questionnaire. A list of terms that are considered "statin-related" (e.g., rhabdomyolysis, acute pancreatitis, myalgia and muscle spasm) will be provided to sites in a manual.

If such an event occurs that meets criteria for serious adverse event, the investigator will complete a separate questionnaire for a Hepatotoxicity and Statin-related Event form (provided by Novartis) to summarize the event, its further diagnostic tests performed, and its related information.

6.5.10 Appropriateness of safety measurements

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

6.6 Other assessments

6.6.1 Patient Reported Outcomes (PRO)

The following Patient reported outcomes (PROs) will be used in the study:

6.6.1.1 IIEF-5

The IIEF-5 score will be used in male patients with heart failure with reduced ejection fraction to determine the patients'/subjects' eligibility for study participation. The IIEF-5 consists of 5 items. For every item, 5 possible response options are available (score 1-5) adding up to a maximum total score of 25. Erectile function will be determined by study personnel by adding individual scores to a total score.

22-25	No erectile dysfunction
17-21	Mild erectile dysfunction
12-16	Mild to moderate erectile dysfunction
8-11	Moderate erectile dysfunction
5-7	Severe erectile dysfunction.

The estimated completion time is 5-10 minutes. The IIEF-5 score will be assessed at Visit 1 and Visit 2.

6.6.1.2 IIEF-15

The IIEF-15 score will be used in male patients with heart failure with reduced ejection fraction. The IIEF-15 is a validated, multi-dimensional, self-administered questionnaire for the

assessment of erectile function. The questionnaire of 15 items organized in 5 domains. The respective domains are:

- Erectile function
- Orgasmic function
- Sexual desire
- Intercourse satisfaction
- Overall satisfaction

For every item 5 possible response options are available (score 1-5) resulting in a maximum score of 75. Erectile function will be determined by study personnel by adding individual scores to a total score.

The estimated completion time is around 10-20 minutes. The IIEF-15 will be assessed at Visit 2 (Randomization) for baseline and at Visits 3, 4, 5 (end of study) and in case of PD or TSD.

[redacted]

6.6.1.4 Patient-reported sexual activity

The patient's sexual activity will be assessed via an electronic diary completed by the patient on a weekly basis. The questionnaire is organized in seven items assessing sexual activity and overall satisfaction with the patient's sexual activity.

The estimated completion time for the sexual activity diary is around 10-15 minutes. The sexual activity diary will be assessed at Visit 2 (Randomization) for baseline and once a week throughout the study.

All PRO measures will be performed as ePROs on an electronic device (tablet). All these questionnaires should be completed by patients/subjects before they see the study physician where applicable. All questionnaires will be completed in German language. IIEF-15 [redacted] will be assessed at the planned study visits 2, 3 and 5 and ideally prior to the patient seeing the investigator for any clinical assessment or evaluation. The patient should be given sufficient instruction, space, time and privacy to complete the questionnaire.

If patients/subjects experience any difficulties with submission after they complete the PROs, the study staff should assist them with submitting their PRO responses. All attempts should be made to collect responses to all PROs for all patients/subjects, including from those who prematurely discontinue prior to the study evaluation completion visit, however, if patients/subjects refuse to complete PROs, this should be documented in study source records. Patient's refusal to complete study PROs are not protocol deviations.

Completed questionnaires will be reviewed and examined by the investigator, before the clinical examination, for responses that may indicate potential adverse events (AEs) or serious adverse events (SAEs). If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 7.1 and Section 7.2 of the protocol.

6.6.2 Pharmacokinetics

Not applicable.

6.6.3 Other biomarkers

Not applicable.

7 Safety monitoring

7.1 Adverse events

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

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

The occurrence of adverse events must be sought by non-directive questioning of the 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 patients and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in **Appendix 1**.

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 7.2** 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 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB

updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

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

7.2 Serious adverse events

7.2.1 Definition of SAE

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - 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.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to Novartis 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 Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

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

7.3 Liver safety monitoring

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

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

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring should be entered into the appropriate CRFs. Please refer to **Table 14-1** in **Appendix 2** for complete definitions of liver laboratory triggers and liver events.

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

For the liver laboratory trigger:

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

These LFT repeats must be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. LFT repeats must then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the appropriate CRFs.

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

For the liver events:

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

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

7.4 Renal safety monitoring

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

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

- new onset (≥1+), hematuria or glycosuria

Every renal laboratory trigger or renal event as defined in **Table 15-1** in **Appendix 3** should be followed up by the investigator or designated personnel at the trial site as summarized in **Appendix 4**.

7.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the 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 7-1 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

7.6 Pregnancy reporting

Not applicable.

7.7 Prospective suicidality assessment

All SAEs relating to suicidal behavior must be reviewed by the Safety Management Team or early project teams.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy

of data capture/data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

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

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRFs) using fully validated secure web-enabled software that conforms to US CFR 21 Part 11 requirements. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

The study will use electronic source documents and source data, and data entry will be done by the sites directly into eSource DDE.

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

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

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Diary data will be entered into an electronic diary by the patient and patients will fill in their PRO data in a site based tablet. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis personnel (or designated CRO).

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

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

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

8.4 Data Monitoring Committee

Not required.

8.5 Angioedema Adjudication Committee

If an angioedema or angioedema-like event occurs, the investigator will complete an Adjudication Questionnaire for an Angioedema-like Event form (provided by Novartis). Details on the process of reporting angioedema and angioedema like events are outlined in a manual provided to investigators.

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

The membership and responsibilities of the Angioedema Adjudication Committee are defined in a separate document that will be provided to the sites.

9 Data analysis

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

9.1 Analysis sets

The following analysis sets will be used for the statistical analyses:

The full analysis set (FAS) will consist of all randomized patients who received at least one dose of study drug. Following the intent-to-treat principle, patients will be analyzed according to the treatment which they were assigned to at randomization. Efficacy variables will be analyzed based on the FAS.

The safety set (SAF) will consist of all randomized patients who received at least one dose of study drug. Patients will be analyzed according to the treatment actually received. The SAF will be used for the analyses of safety variables.

9.2 Patient demographics and other baseline characteristics

Baseline value is defined as the last non-missing assessment prior to the first dose of randomized study medication.

Summary statistics will be provided by treatment group for demographics and baseline characteristics, including age, age group (<65 years vs. ≥65 years), sex, race, weight, height, body mass index (BMI), category of prior CHF medication, prior HF hospitalization, NYHA class, and vital signs. BMI will be calculated as weight (kg) / height2 (m2) from the collected height and weight at Visit 1 (Screening). Continuous variables will be summarized using n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency and percentage. The FAS will be the patient population for the above analyses.

9.3 Treatments

The overall duration on the double-blind study drug will be summarized by treatment group using mean, standard deviation, median, minimum, and maximum. Additionally, the number and percentage of patients will be summarized by treatment group for duration category.

Concomitant medications and significant non-drug therapies, prior to and after the randomization date respectively, will be summarized by therapeutic class, preferred term, and treatment group for the safety population.

The number and percentage of patients on different CHF background medications (β-blockers, diuretics) will be tabulated by treatment at baseline and during the double-blind stage.

The FAS will be used for the above analyses.

9.4 Analysis of the primary variable(s)

9.4.1 Primary Variable(s)

The primary endpoint is the Erectile function score IIEF-15 at 3 months. The trial aims to estimate the effect of the treatment policy, irrespective of intercurrent events such as dose changes or adherence to randomized treatment. The following estimand will be used:

- Population – Full Analysis Set (FAS)
- Variable of Interest – Erectile function score IIEF-15 at 3 months
- Intervention effect – effect between sacubitril/valsartan versus enalapril at 3 months regardless of adherence to randomized treatment.
- Summary measure –difference in means

For patients who permanently discontinue study treatment, values collected after study drug discontinuation will generally be included in the analysis.

9.4.2 Statistical model, hypothesis, and method of analysis

The primary variable will be analyzed using a mixed model for repeated measures (MMRM), The response variable will be the Erectile function score IIEF-15. Treatment (sacubitril/valsartan versus enalapril), visit and treatment-by-visit interaction will be included as fixed-effect factors; baseline IIEF-15 will be included as a covariate; the within-patient covariance will be modeled using an unstructured covariance matrix (a common matrix for the two treatment groups). The analysis will include all (two) scheduled post-baseline visits and will be performed based on the likelihood method with an assumption of missing at random (MAR) for missing data.

The null-hypothesis to be rejected is that there is no difference in mean IIEF-15 scores at 3 months between the two treatment arms, in mathematical terms: H_0: $\mu_1 = \mu_2$ vs. H_a: $\mu_1 \neq \mu_2$, where μ_1 and μ_2 are mean IIEF-15 scores at 3 months for the treatment groups of sacubitril/valsartan versus enalapril, respectively.

The statistical test will be performed at the two-sided significance level of 0.05 based on the MMRM model. The estimates and the corresponding 95% confidence intervals will be provided for the difference in adjusted means at month 3 between the two treatment groups based on the MMRM model. Although this test is defined as two-sided, superiority of sacubitril/valsartan versus enalapril will be claimed only, if the difference is in favor of sacubitril/valsartan.

The FAS will be used for the above primary analyses.

9.4.3 Handling of missing values/censoring/discontinuations

Patients will be followed up and all scheduled visits should be performed, even if study drug is discontinued for that respective patient prematurely. Therefore, missing values should only

occur in case of death, withdrawal of informed consent or loss to follow up. In these cases, patients will be included with their available values into the statistical MMRM model.

9.4.4 Sensitivity analyses

A 'while on treatment' estimand might be meaningful to explore the effect of drop-outs on the primary estimand. This estimand will include drop-outs with their last observed value and will not (like the MMRM model of the primary estimand) extrapolate a possible improvent that might have been observed if the patient had continued. The following estimand will be used:

- Population – Full Analysis Set (FAS)
- Variable of Interest – Erectile function score IIEF-15 at last observed visit
- Intervention effect – effect between sacubitril/valsartan versus enalapril at last observed visit regardless of adherence to randomized treatment.
- Summary measure – difference in means

For patients for whom an IIEF-15 at month 3 is available, this value will be used, regardless of adherence to treatment. Analysis will be performed using an Analysis of Covariance model for IIEF-15 at last observed visit with factor treatment group and covariate baseline IIEF-15.

In case of substantial/early drop-out, additional estimands may be explored as post-hoc analyses.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

Self-reported frequency of sexual activity per month will be analyzed using a MMRM model analogous to the one used for the primary endpoint, NT-proBNP levels at months 1 and 3 will be summarized descriptively using n, mean, standard deviation, median, minimum, and maximum.

9.5.2 Safety variables

Safety assessments will be based mainly on the frequency of adverse events. Adverse events will be coded by primary system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). An adverse event related to study drug is defined as one considered by the investigator to have a suspected relationship with the study drug. The adverse events will be summarized by the number and percentage of patients in each primary system organ class and preferred term. For summaries by severity of event, the most severe occurrence for a particular preferred term will be used for a given patient. Summary tables of adverse events by treatment and severity will be provided.

Multiple occurrences of the same AE or SAE in the same patient will be counted only once, using the worst severity and drug relationship.

In the data listings of adverse events, the severity of an AE, whether or not an AE is study drug related, and whether or not it is a serious AE, will be indicated.

Laboratory data will be summarized by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges) and by presenting number and percentage of patients with notable laboratory abnormalities according to **Appendix 1**.

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

9.5.3 Resource utilization

Not required.

9.5.4 Pharmacokinetics

Not applicable

9.5.5 DNA

Not applicable.

9.5.6 Biomarkers

Not applicable

9.5.7 PK/PD

Not applicable.

[redacted]

9.7 Interim analyses

Not applicable, no interim analysis will be performed.

9.8 Sample size calculation

For the IIEF-15 domain "erectile function", the treatment effect and SD of sacubitril/valsartan compared to enalapril was estimated based on the previous VALED study, which demonstrated that valsartan showed a highly significant increase in erectile function from 16.54±8.27 to 23.14±6.49 IIEF units in hypertensive males (Dusing, 2003). VALED was an open-label study comparing 6 months treatment with valsartan to baseline. CONFIDENCE on the other hand is

a double-blind randomized trial and the beneficial effect of sacubitril/valsartan will likely be driven not by valsartan but by the neprilysin inhibition introduced by sacubitril. For sample size calculation the shorter study period, differing patient population (heart failure versus hypertension) as well as the use of bisoprolol/metoprolol have to be taken into account. Beta-blocker have differing effects on erectile function. While propranolol and atenolol are well-known to reduce sexual function, nebivolol has vasodilating effects, which may even be beneficial in erectile dysfuntion (Baumhakel et al., 2011). Bisoprolol/metoprolol have been suggested to have a neutral effect on erectile dysfunction (Baumhakel et al., 2011) and were thus chosen as the allowed concomitant beta-blockers within the study.

Therefore, a treatment effect of sacubitril/valsartan compared to enalapril of 3.5 IIED units was estimated. Assuming a standard deviation of 7 IIEF units and a two-sided alpha of 0.05, 86 patients per arm would confer a 90% power to detect a conservative treatment difference of 3.5 IIEF units. This is in accordance with the minimal clinically important difference of the erectile function domain of IIEF-15 of 2 and 5 IIEF units in patients with mild and moderate erectile dysfunction, respectively (Rosen et al., 2011).

To compensate for some drop-out and other protocol deviations, 100 patients/arm (200 in total) should be randomized into this trial. There will be no additional recruitment in case some patients will not be able to achieve the target dose since based on PARADIGM-HF and a shorter trial duration, no substantial influence on the power of the trial is expected.

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if applicable after such consent has been provided by a legally acceptable representative(s) of the patient. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

For trials using an Electronic Informed Consent system where a date/timestamp is automatically generated, the system-generated date/timestamp is sufficient; additional input of the date at the time of consent is not required by the patient.

Novartis will provide to investigators in a separate document an informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study.

10.3 Responsibilities of the investigator and IRB/IEC

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

10.4 Publication of study protocol and results

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

10.5 Quality Control and Quality Assurance

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

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

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

11 Protocol adherence

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

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

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients/subjects may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

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13 Appendix 1: Clinically notable laboratory values

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

Hematology	
RBC count	>50% increase, >20% decrease
Hemoglobin	>50% increase, >20% decrease
Hematocrit	>50% increase, >20% decrease
WBC count	>50% increase, >50% decrease
Platelet count	>75% increase, >50% decrease
Blood Chemistry	
ALT (SGPT)	>150% increase
AST (SGOT)	>150% increase
BUN	>50% increase
Creatinine	>50% increase
Total bilirubin	>100% increase
CPK	>300% increase
Alkaline phosphatase	>100% increase
Potassium	>20% increase, >20% decrease
Chloride	>10% increase, >10% decrease
Calcium	>10% increase, >10% decrease
Uric acid	>50% increase

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

Table 14-1 Liver Event and Laboratory Trigger Definitions

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

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

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

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

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

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

15 Appendix 3: Specific Renal Alert Criteria and Actions

Table 15-1 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider patient hospitalization /specialized treatment
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnos ic procedures performed Monitor patient regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.	

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

General principles

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

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

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

Corrective action for management of hyperkalemia

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

- Confirm potassium concentration in a non-hemolyzed sample
- Reinforce low potassium diet and restriction of food/drinks with high potassium content (e.g. orange juice, melon, bananas, low-salt substitutes etc.)
- Review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia. Consider reduction in dose or discontinuation of these agents:

- Aldosterone antagonists (if they are believed to be the most likely cause of hyperkalemia)
- Potassium-sparing diuretics (e.g. amiloride and triamterene) including in combination products with thiazide or loop diuretics
- Potassium supplements, e.g., potassium chloride
- Salt substitutes
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Cyclo-oxygenase-2 (COX-2) inhibitors
- Trimethoprim and trimethoprim-containing combination products, such as trimethoprim/sulfamethoxazole fixed combinations
- Herbal Supplements: For example, Noni juice, alfalfa (Medicago sativa), dandelion (Taraxacum officinale), horsetail (Equisetum arvense), nettle (Urtica dioica), milkweed, lily of the valley, Siberian ginseng, hawthorn berries
- Repeat serum potassium measurement within 3 to 5 days
- If serum potassium remains ≥ 5.3 and ≤ 5.5 mmol/L, regularly monitor serum potassium levels to ensure stability (suggested once monthly).
- Consider down-titration of study medication, according to investigator's medical judgment.
- Consider down-titration or temporarily discontinue study drug according to investigator medical judgment.
- If serum potassium < 5.5 mmol/L, consider resumption of study drug at lower dose with repeat potassium within 3-5 days

Serum potassium greater than or equal to 6.0 mmol/L

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

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

17 Appendix 5: Guidelines for the management of blood pressure

Guidelines:

1. Investigator should monitor blood pressure closely
2. If symptomatic hypotension occurs:
    a. Correct any treatable cause, e.g. hypovolemia
    b. If hypotension persists, any antihypertensive drug and non-disease-modifying drugs, such as diuretics, CCBs, nitrates, and α-blockers, should be down titrated or stopped first before down-titration of the study drug is considered
    c. If hypotension persists, the study drug should be down titrated or even temporarily withdrawn. The dose re-challenge and medications adjust guidelines described in Section 5.5.5 should be adhered to as much as possible.

18 Appendix 6: Guidelines for the management of renal dysfunction

General principles:

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

Two types of response to serum creatinine increase are described:

Surveillance situation

If, at any time after randomization, eGFR decreases by ≥ 25% from baseline (Visit 2) (or if serum creatinine concentration increases to 2.5 mg/dL [221 μmol/L]), the investigator will check for potentially reversible causes of renal dysfunction such as:

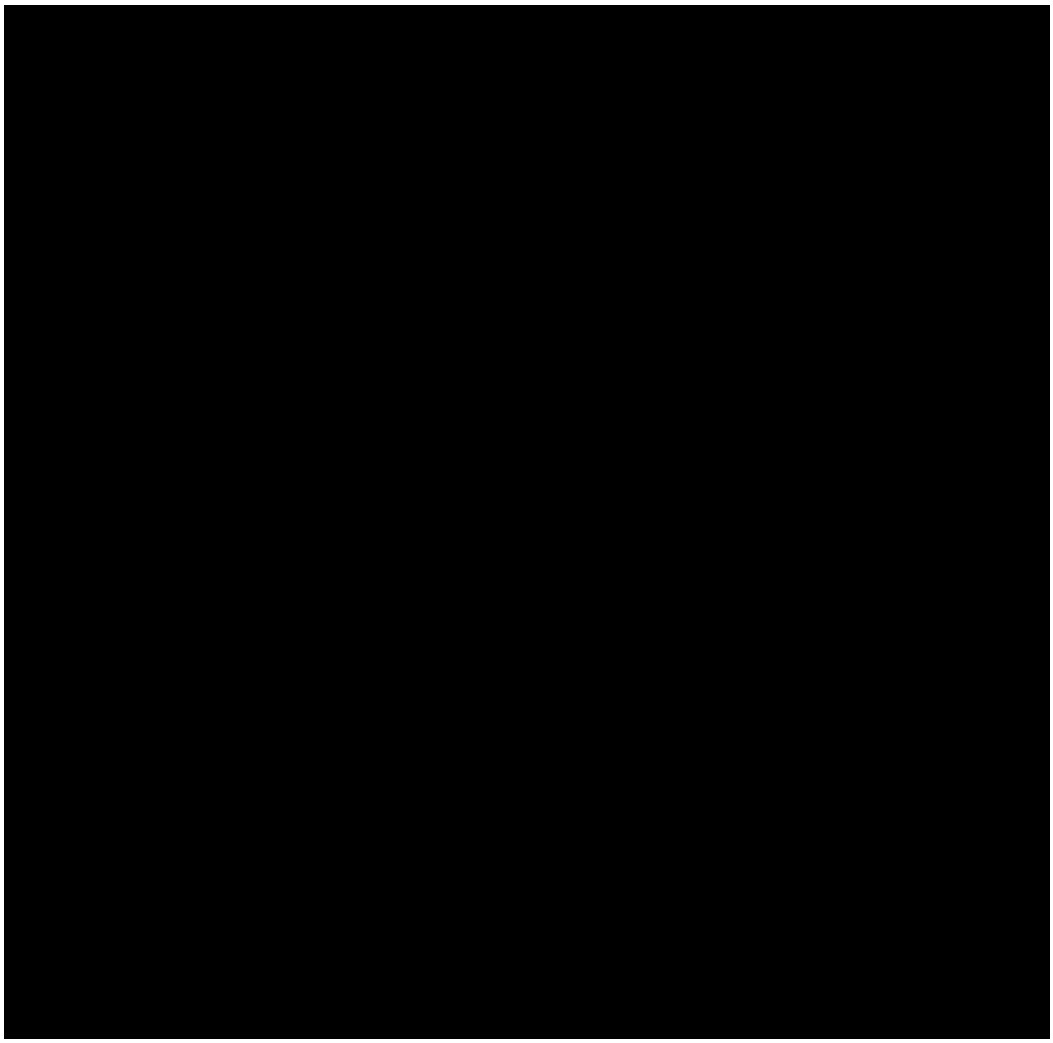
- Non-steroidal anti-inflammatory drug intake, antibiotics, or other treatments known to affect serum creatinine levels
- Volume decrease, including that resulting from excessive dosing of diuretics
- Urinary infection

- Urinary tract obstruction
- Study medication

Action situation

If a patient eGFR decreases by ≥ 40% from baseline (Visit 2) (or if serum creatinine concentration rises above 3 mg/dL (265 µmol/L)), the investigator will check for potentially reversible causes of renal dysfunction (see above).

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



20 Appendix 8: IIEF-5

INTERNATIONAL INDEX FOR ERECTILE DYSFUNCTION (IIEF-5)

Over the past 4 weeks:

1.	How do you rate your **confidence** that you could get and keep an erection?	1 Very low	2 Low	3 Moderate	4 High	5 Very high
2.	When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	1 Almost never/never	2 A few times (much less than half the time)	3 Sometimes (about half the time)	4 Most times (much more than half the time)	5 Almost always/always
3.	During sexual intercourse, **how often** were you able to maintain your erection after you had penetrated (entered) your partner?	1 Almost never/never	2 A few times (much less than half the time)	3 Sometimes (about half the time)	4 Most times (much more than half the time)	5 Almost always/always
4.	During sexual intercourse, **how difficult** was it to maintain your erection to completion of intercourse?	1 Extremely difficult	2 Very difficult	3 Difficult	4 Slightly difficult	5 Not difficult
5.	When you attempted sexual intercourse, how often was it satisfactory for you?	1 Almost never/never	2 A few times (much less than half the time)	3 Sometimes (about half the time)	4 Most times (much more than half the time)	5 Almost always/always

[a]The IIEF-5 score is the sum of the ordinal responses to the five items; thus, the score can range from 5 to 25.

21 Appendix 9: IIEF-15

INTERNATIONAL INDEX FOR ERECTILE DYSFUNCTION (IIEF-15)

These questions ask about the effect your erection problems have had on your sex life over the past 4 weeks. Please answer these questions as honestly and as clearly as possible. Please answer every question by checking the appropriate box [✓]. If you are unsure about how to answer, please give the most accurate answer you can.

In answering these questions, the following definitions apply:

* **Sexual intercourse**

Is defined as vaginal penetration (entry) of the partner.

** **Sexual Activity**

Includes sexual intercourse, caressing, foreplay and masturbation.

*** **Ejaculate**

Is defined as the ejection of semen from the penis (or the sensation of this).

**** **Sexual stimulation**

Includes situations such as loveplay with a partner, looking at erotic pictures, etc.

1. **Over the past 4 weeks** how often were you able to get an erection during sexual activity**?
Please check one box only.

- No sexual activity ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

2. **Over the past 4 weeks** when you had erections with sexual stimulation****, how often were your erections hard enough for penetration?
Please check one box only.

- No sexual stimulation ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

The next 3 questions will ask about the erections you may have had during sexual intercourse*.

3. **Over the past 4 weeks** when you attempted sexual intercourse* how often were you able to penetrate (enter) your partner?
Please check one box only.

- Did not attempt to initiate sexual intercourse ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

4. **Over the past 4 weeks** during sexual intercourse* how often were you able to maintain your erection after you had penetrated (entered) your partner?
Please check one box only.

- Did not attempt to initiate sexual intercourse ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

5. **Over the past 4 weeks** during sexual intercourse* **how difficult** was it to maintain your erection to completion of intercourse?
Please check one box only.

- Did not attempt to initiate sexual intercourse ☐
- Extremely difficult ☐
- Very difficult ☐
- Difficult ☐
- Slightly difficult ☐
- Not difficult ☐

* **Sexual intercourse:** Is defined as vaginal penetration (entry) of the partner
** **Sexual activity:** Includes sexual intercourse, caressing, foreplay and masturbation
*** **Ejaculate:** Is defined as the ejection of semen from the penis (or the sensation of this)
**** **Sexual stimulation:** Includes situations such as loveplay with a partner, looking at erotic pictures, etc

6. **Over the past 4 weeks** how many times have you attempted sexual intercourse*?
Please check one box only.

- No attempts ☐
- 1-2 attempts ☐
- 3-4 attempts ☐
- 5-6 attempts ☐
- 7-10 attempts ☐
- 11 and more attempts ☐

7. **Over the past 4 weeks** when you attempted sexual intercourse* how often was it satisfactory for **you**?
Please check one box only.

- Did not attempt to initiate sexual intercourse ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

8. **Over the past 4 weeks** how much have you enjoyed sexual intercourse*?
Please check one box only.

- No sexual intercourse ☐
- Very highly enjoyable ☐
- Highly enjoyable ☐
- Fairly enjoyable ☐
- Not very enjoyable ☐
- Not enjoyable ☐

* **Sexual intercourse:** Is defined as vaginal penetration (entry) of the partner
** **Sexual activity:** Includes sexual intercourse, caressing, foreplay and masturbation
*** **Ejaculate:** Is defined as the ejection of semen from the penis (or the sensation of this)
**** **Sexual stimulation:** Includes situations such as loveplay with a partner, looking at erotic pictures, etc

9. **Over the past 4 weeks** when you had sexual stimulation**** **or** had sexual intercourse* how often did you ejaculate***?
Please check one box only.

- No sexual stimulation or intercourse ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

10. **Over the past 4 weeks** when you had sexual stimulation**** **or** had sexual intercourse* how often did you have the feeling of orgasm with or without ejaculation***?
Please check one box only.

- No sexual stimulation or intercourse ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

* **Sexual intercourse:** Is defined as vaginal penetration (entry) of the partner
** **Sexual activity:** Includes sexual intercourse, caressing, foreplay and masturbation
*** **Ejaculate:** Is defined as the ejection of semen from the penis (or the sensation of this)
**** **Sexual stimulation:** Includes situations such as loveplay with a partner, looking at erotic pictures, etc

The next 2 questions ask about sexual desire. Let's define sexual desire as a feeling that may include wanting to have a sexual experience (e.g. masturbation or intercourse*), thinking about sex, or feeling frustrated due to lack of sex.

11. **Over the past 4 weeks** how often have you felt **sexual desire**?
Please check one box only.

- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

12. **Over the past 4 weeks** how would you assess your level of **sexual desire**?
Please check one box only.

- Very high ☐
- High ☐
- Moderate ☐
- Low ☐
- Very low or none at all ☐

* **Sexual intercourse:** Is defined as vaginal penetration (entry) of the partner
** **Sexual activity:** Includes sexual intercourse, caressing, foreplay and masturbation
*** **Ejaculate:** Is defined as the ejection of semen from the penis (or the sensation of this)
**** **Sexual stimulation:** Includes situations such as loveplay with a partner, looking at erotic pictures, etc

13. **Over the past 4 weeks** how satisfied on average have you been with your **sex life**?
Please check one box only.

- Very satisfied ☐
- Moderately satisfied ☐
- About equally satisfied and dissatisfied ☐
- Moderately dissatisfied ☐
- Very dissatisfied ☐

14. **Over the past 4 weeks** how satisfied have you been with your **sexual relationship** with a partner?
Please check one box only.

- Very satisfied ☐
- Moderately satisfied ☐
- About equally satisfied and dissatisfied ☐
- Moderately dissatisfied ☐
- Very dissatisfied ☐

15. **Over the past 4 weeks** how would you rate your **confidence** that you could get and keep an erection?
Please check one box only.

- Very high ☐
- High ☐
- Moderate ☐
- Low ☐
- Very low ☐

* **Sexual intercourse:** Is defined as vaginal penetration (entry) of the partner
** **Sexual activity:** Includes sexual intercourse, caressing, foreplay and masturbation
*** **Ejaculate:** Is defined as the ejection of semen from the penis (or the sensation of this)
**** **Sexual stimulation:** Includes situations such as loveplay with a partner, looking at erotic pictures, etc

22 Appendix 10: Sexual activity diary

1. Within the past 7 days, how often did you try to have sexual intercourse (attempted vaginal penetration) with your partner?

□	not at all (no attempted sexual intercourse within the past 7 days)
□	once
□	twice
□	three times
□	> three times

2. Within the past 7 days, how often have you tried to masturbate?

□	not at all (no attempt to masturbate within the past 7 days)
□	once
□	twice
□	three times
□	> three times

3. Within the past 7 days, how often did you have an erection at night or in the morning (if both apply, please only count once)?

□	not at all (no erection at night or in the morning)
□	once
□	2-3 times
□	4-5 times
□	> 5 times

4. Within the past 7 days, how often have you had intimate physical activity with your partner **other than** having vaginal intercourse (exchange of affection, foreplay, petting, oral intercourse)?

□	not at all (no other sexual activity)
□	once
□	2-3 times
□	4-5 times
□	> 5 times

5. Within the past 7 days, did you avoid physical intimacy with your partner because of your diminished erectile capability?

□	yes
□	no

6. Within the past 7 days, how would you rate your affection/emotions towards your partner?

□	non existent
□	little

□	satisfactory
□	strong
□	very strong

7. Within the past 7 days, to which extent did your sexual desire influence your mood?

□	very negatively affected
□	negative affected
□	not affected
□	positive affected
□	very positive affected

NOVARTIS

Global Clinical Development - General Medicine

sacubitril/valsartan

Clinical Trial Protocol CLCZ696BDE03

A randomized, double-blind, active-controlled study to assess the effect of sacubitril/valsartan compared with enalapril to improve erectile function in patients with heart failure with reduced ejection fraction (HFrEF) and erectile dysfunction (ED)

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	COmparing arNi and ace For Improving erectile Dysfunction in mEN with reduCed Ejection fraction heart failure
	Heart failure (HF) patients typically display various symptoms including peripheral congestion, low exercise tolerance, fatigue and dyspnea, which contribute to a progressive worsening of quality of life (QoL). Additionally, sexual activity remains an essential aspect of QoL, since, contrary to common belief, seriously ill patients mostly do not lose their interest in intimacy. An estimated 70% of male HF patients experience erectile dysfunction (ED). Decreasing left ventricular function is associated with significantly reduced erectile function in cardiovascular high-risk patients and ED was shown to precede cardiovascular events in these patients. A secondary analysis of the Kansas City Cardiomyopathy Questionnaire (KCCQ) used in the PARADIGM-HF trial demonstrated that patients treated with sacubitril/valsartan significantly improved nearly all criteria at the physical limitation and social limitation section when compared with enalapril, with the most significant changes in intimate/sexual relationships after 8 months of double-blind treatment. Based on these beneficial effects and the potential positive influence of enhanced CNP levels under sacubitril/valsartan treatment in erectile tissue, we hypothesize that sacubitril/valsartan may also enhance erectile function in male HFrEF patients, thereby contributing to improvement of QoL. Enhancement in erectile function will be evaluated using the renowned International Index of Erectile Function (IIEF).
	To demonstrate the superiority of sacubitril/valsartan compared to enalapril regarding improvement in erectile function and ability in male patients with chronic heart failure and erectile dysfunction using the questionnaire International index of erectile function (IIEF-15) at the end of the study.
	• To assess the early-onset effect as well as the effect at the end of the study of sacubitril/valsartan versus enalapril regarding improvement in sexual activity assessed using patient's self-reported frequency of sexual activity per month • To assess the early-onset effect as well as the effect at the end of the study of sacubitril/valsartan versus enalapril regarding NT-proBNP levels
	This is a randomized, double-blind, double-dummy, multi-center, active-controlled, interventional study to compare sacubitril/valsartan to enalapril in improving erectile function in

	male patients with chronic heart failure (NYHA II) and reduced ejection fraction (HFrEF) and erectile dysfunction (ED).
	The study population will consist of a representative group of adult (≥18 and ≤ 75) male HFrEF patients in NYHA class II with mild to moderate ED. Eligible patients should be on a stable dose of an ACEI or an ARB as well as bisoprolol/metoprolol for at least 4 weeks prior to randomization. The targeted projected sample size is 200 patients (100 patients in each arm). It is expected that 286 patients will be screened at up to approximately 40 study sites, as a screen failure rate of 30% is anticipated.
	• Patients must give written informed consent before any assessment is performed and must be willing and capable to comply with all study procedures • Male Outpatients ≥ 18 and ≤ 75 years of age • Patients with a diagnosis of CHF NYHA class II and reduced ejection fraction (< 40%) at Visit 1 • Plasma NT-proBNP level of ≥ 300 pg/mL at Visit 1(Screening) • Patients must be living in a stable and sexually active heterosexual partnership for at least 6 months prior to Visit 1 • Patients must have a mild to moderate erectile dysfunction determined using the IIEF-5 questionnaire (> 7 and ≤ 21 IIEF units) at Visit 1 (Screening) and Visit 2 (Randomization) • Patients must be on an ACEI or ARB at a stable dose for at least 2 weeks prior to Visit 1 and 4 weeks prior to Visit 2 • Patients must be treated with a stable dose of bisoprolol/metoprolol for at least 2 weeks prior to Visit 1 and 4 weeks prior to Visit 2 • No usage of any available drug for erectile dysfunction (e.g. sildenafil, tadalafil) for at least 2 weeks prior to Visit 1 and 4 weeks prior to Visit 2
	• History of hypersensitivity or allergy to any of the study drugs, drugs of similar chemical classes, ACEIs, ARBs, or NEP inhibitors as well as known or suspected contraindications to the study drugs • Previous history of intolerance to recommended target doses of ACEIs or ARBs • Known history of angioedema • Requirement of treatment with both ACEIs and ARBs • Current acute decompensated HF (exacerbation of chronic HF manifested by signs and symptoms that may require intravenous therapy)

	• Symptomatic hypotension and SBP ≤100 mm Hg at Visit 1 (Screening) or Visit 2 (Randomization) • Estimated glomerular filtration rate (eGFR) below 30mL/min/1.73m^2 at Visit 1 (Screening) or Visit 2 (Randomization) • Serum potassium level of more than 5.2 mmol/L at Visit 1 (Screening) or Visit 2 (Randomization) • History of severe pulmonary disease • Penile anatomical defects and Peyronie's disease • Foreseeable usage of any available drug for erectile dysfunction (e.g. sildenafil, tadalafil) during the trial • Prostate-specific antigen (PSA) levels higher than 4 ng/mL at Visit 1 or known prostate cancer
	• Placebo to match sacubitril/valsartan at all dose levels • Enalapril (target dose 10 mg bid) • Placebo to match enalapril at all dose levels
	• IIEF-15 questionnaire • Patient-reported frequency of sexual activity • Changes in NT-proBNP [redacted]
	• Adverse event monitoring • Physical examinations and blood pressure monitoring • Monitoring of laboratory markers in blood (potassium, creatinine, AST/ALT)
	The primary variable will be analyzed using a mixed model for repeated measures (MMRM). The response variable will be the Erectile function score IIEF-15. Treatment (sacubitril/valsartan versus enalapril), visit and treatment-by-visit interaction will be included as fixed-effect factors; baseline IIEF-15 will be included as a covariate. Secondary endpoints will be analyzed descriptively.

Amendment 1

Amendment Rationale

This amendment is being introduced as a consequence of feedback from Health Authorities. In summary, the classification of the clinical phase of the trial was adjusted. In addition, exclusion criterion 33 was modified and the end of the study was defined in more detail.

A copy of this amended protocol will be sent to the Independent Ethics Committee and Health Authorities.

Changes to the protocol

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

Clinical Trial Phase:

This trial is classified as a phase IIIB trial instead of phase IV

Section 4.2

Exclusion criterion 33 was modified, extending the exclusion also to patients in which any neurodegenerative disease or polyneuropathy is suspected.

Section 5.6.1

The end of the study was defined in more detail. The trial as a whole will be considered completed when the last visit of the last subject occurred.

1. Introduction

1.1 Background

Heart failure (HF) patients typically display various symptoms including peripheral congestion, low exercise tolerance, fatigue and dyspnea, which contribute to a progressive worsening of quality of life (QoL). Additionally, sexual activity remains an essential aspect of QoL, since, contrary to common belief, seriously ill patients mostly do not lose their interest in intimacy (Alberti et al., 2013). The American Heart Association asserts that sexual activity is appropriate and safe for patients with compensated and/or mild HF (NYHA I/II) (Levine et al., 2012) but unfortunately, an estimated 70% of male HF patients experience erectile dysfunction (ED) (Alberti et al., 2013). ED describes the persistent inability to achieve and/or maintain a penile erection sufficient for satisfactory sexual performance (Lue, 2000).

ED and HF share common risk factors including age, atherosclerosis, hyperlipidemia, hypertension, diabetes mellitus, smoking, obesity and sedentary lifestyle (Rastogi et al., 2005). Decreasing left ventricular function is associated with significantly reduced erectile function in cardiovascular high-risk patients and ED was shown to precede cardiovascular events in these patients (Baumhakel and Bohm, 2007). In addition, common underlying pathophysiological mechanisms such as atherosclerosis causing reduced blood-flow, arterial insufficiency and endothelial dysfunction are anticipated to contribute to both ED and HF progression (Rastogi et al., 2005). Furthermore, ED is also influenced by depression, exercise tolerance impairment, anabolic deficiency and pharmacological treatment (Alberti et al., 2013).

Several physiological pathways contribute to developing an erection. Contracted penile smooth muscle cells (SMC) in cavernosal arterioles and sinuses have to be transferred into the relaxed state in order to facilitate vasodilation and blood influx into the corpora cavernosa. With the increased intracorporal pressure, the surrounding fibrous tunica albuginea is stretched and thus compresses the subtunical venules. Thereby, the venous outflow is tremendously reduced contributing to initiation and maintenance of an erection (Fraga-Silva et al., 2013).

Sexual stimulation triggers nitric oxide (NO) release from penile nerves and activates the soluble guanyl cyclase (GC) in penile SMC to catalyze the conversion of GTP to cGMP. This results in the relaxation of SMCs and an increased blood flow into penile tissue.

Besides this well-known mechanism, the particulate guanyl cyclase (pGC), a cytoplasmic membrane-bound GC, additionally plays a pivotal role in erectile tissue. pGC is activated by binding of the C-type natriuretic peptide (CNP) to its receptor NPR-B. Subsequently, active pGC converts GTP to cGMP in penile SMCs (Kuthe et al., 2003). Additionally, CNP acts as an endothelium-derived hyperpolarizing factor (EDHF) and binding to its other receptor NPR-C elicits an activation of the inward rectifier K+ channel mediating the hyperpolarization and relaxation of penile SMCs (Kun et al., 2008). Thus, CNP essentially contributes to maintaining SMCs dilated and the penile tissue erect. ED patients display significantly lower NT-proCNP levels, which correlates with the erectile function assessed using the International index of erectile function (IIEF-5) (Vlachopoulos et al., 2010).

Furthermore, the RAAS system has been identified to play a paracrine role in penile tissue and interestingly, the physiological amount of angiotensin II produced in erectile tissues exceeds that found in the systemic plasma (Fraga-Silva et al., 2013). Angiotensin II elicits penile SMC

contraction by binding to its AT1 receptor. Consequently, angiotensin II contributes to the detumescence of the penis and termination of an erection. A hyperactivity of this peptide is known to augment the pathogenesis of ED (Becker et al., 2001).

Sacubitril/valsartan is a first-in-class angiotensin receptor-neprilysin inhibitor (ARNI), which both blocks the RAAS and augments natriuretic peptides, and was developed for the treatment of chronic HF. The clinical efficacy of sacubitril/valsartan in HF with reduced ejection fraction (HFrEF) patients has been demonstrated in the PARADIGM-HF study (McMurray et al., 2014). Sacubitril/valsartan not only established a significant benefit over enalapril in reducing cardiovascular death and hospitalizations due to HF as well as all-cause mortality, it also improved both health-related QoL, measured by Kansas City Cardiomyopathy Questionnaire (KCCQ) and EQ-5D, as well as symptom burden measured by NYHA class (Packer et al., 2015, McMurray et al., 2014). Furthermore, a post-hoc analysis of KCCQ demonstrated that patients treated with sacubitril/valsartan significantly improved nearly all criteria at the physical limitation and social limitation section when compared with enalapril, with the most significant changes in intimate/sexual relationships after 8 months of double-blind treatment persisting throughout 36 months (Chandra et al., 2018).

Based on these beneficial effects and the potential positive influence of enhanced CNP levels in erectile tissue, we hypothesize that sacubitril/valsartan may also enhance erectile function in male HFrEF patients, thereby contributing to improvement of QoL. Enhancement in erectile function will be evaluated using the renowned International Index of Erectile Function (IIEF), which was developed and validated in the 1990s and used in various clinical trials (Rosen et al., 1997, Wiltink et al., 2003). Since the questionnaire was developed for heterosexual men with the assumption of vaginal sex, homosexuals unfortunately cannot be included in this trial.

[redacted]**urpose**

The purpose of this study is to evaluate the effect of sacubitril/valsartan in improving erectile function in male patients with chronic heart failure (NYHA II) and reduced ejection fraction (HFrEF) and erectile dysfunction (ED). Data from this study are intended to provide a thorough understanding of the impact of sacubitril/valsartan on male sexual function and therefore quality of life.

2. Study objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**

Objective(s)	Endpoint(s)
• To demonstrate the superiority of sacubitril/valsartan compared to enalapril regarding improvement in erectile function and ability in male patients with chronic heart failure and erectile dysfunction using the questionnaire International Index of Erectile Function (IIEF-15) at the end of the study	• Erectile function score at 3 months

Secondary Objective(s)	Endpoint(s) for secondary objective(s)
• To assess the early-onset effect as well as the effect at the end of the study of sacubitril/valsartan versus enalapril regarding improvement in sexual activity assessed using patient's self-reported frequency of sexual activity per month	• Self-reported frequency of sexual activity per month at months 1 and 3
• To assess the early-onset effect as well as the effect at the end of the study of sacubitril/valsartan versus enalapril regarding NT-proBNP levels	• NT-proBNP levels at months 1 and 3

3. Investigational plan

3.1 Study design

This is a randomized, double-blind, double-dummy, multi-center, active-controlled, interventional study to compare sacubitril/valsartan 97 mg/103 mg bid to enalapril 10 mg bid in improving erectile function in male patients with chronic heart failure (NYHA II) and reduced ejection fraction (HFrEF) and erectile dysfunction (ED).

The study comprises five obligatory and one optional visit over a period of approximately 14 weeks. Once patients' eligibility has been ascertained at Visit 1 (Screening), patients will be randomized at Visit 2 (Randomization) to receive either sacubitril/valsartan or enalapril in a 1:1 allocation during the double-blind period. At Visit 2, all efficacy assessments will be collected and used as baseline values. Double-blind treatment will be initiated with 5 mg bid enalapril or 49 mg/51 mg bid sacubitril/valsartan and up-titrated after 2 weeks to the final dose of 10mg bid enalapril or 97 mg/103 mg bid sacubitril/valsartan. According to the sacubitril/valsartan SmPC, initiation of treatment is recommended with the 24 mg/26 mg bid sacubitril/valsartan or 2.5 mg bid enalapril dose for certain patients. For these patients, an optional visit 4B after achieving the target dose of 97 mg /103 mg bid sacubitril/valsartan or 10 mg bid enalapril is mandatory. For allowed investigational treatment dose adjustments during double-blind period refer to **Section 5.5.4**.

All laboratory evaluations for planned visits and for unscheduled visits will be performed by the central laboratory. In order to have the results from the central laboratory available and enable a competent decision on randomization or up-titration at the respective visits, patients should come to the site approximately 3 to 4 days prior to the scheduled visit date for a blood draw (applies for Visit 2 (Randomization), Visit 3 and Visit 4 (Cave: Visit 4: safety lab only for patients who started with dose level 1)).

Further information on the visit schedule and data collection scheme can be found in**Table 6-1**.

Visit 1 (Screening)

At Visit 1 (-2 to -1 weeks) after signing informed consent, the inclusion and exclusion criteria will be checked for each patient to ascertain eligibility (see Section **4**). Among other criteria, they have been on a stable dose of enalapril of at least 10 mg/d, or equivalent ACEI or ARB for at least 4 weeks prior to visit 1 (see **Table 2-1**). A complete physical examination is required at Visit 1. Mild to moderate ED will be determined using a short form of the International Index of Erectile Function (IIEF-5). Screening potassium levels and eGFR as well as the biomarker NT-proBNP will be assessed by sending blood samples to the central laboratory and only patients with the required values per entry criteria will be eligible for entering the study. Detailed HF history and other relevant CV medical history will be recorded on eCRFs separately from other medical history.

The investigator may consider re-screening the patient at a later time if he/she believes that the patient's condition has changed and the patient may potentially be eligible. A minimum of 2 weeks must elapse between re-screenings and a patient may be re-screened once only (see **Section 6.1**).

Patients will continue stable intake of their current ACEI/ARB as well as concomitant medication until Visit 2 (Randomization). They should be reminded to come without taking their usual ACEI to Visit 2. For ACEI a **wash-out period of ≥ 36 hours** before first application of investigational treatment is mandatory.

Table 3-1 Minimum required pre-study daily doses of commonly prescribed ACEIs and ARBs

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

Visit 2 (Randomization)

At Visit 2 (timepoint 0), patients who meet all relevant entry criteria, including the required clinical laboratory values and safety criteria, will be randomized to one of the two treatment arms sacubitril/valsartan or enalapril bid, respectively. Patients should continue to take their background medication for heart failure during the study, with the exception of ACEI or ARBs which are replaced by the investigational treatment and must be discontinued before first application of the study drug (**washout period of ≥ 36 hours is mandatory for ACEI**). The first application of the study drug is planned for the day after Visit 2 (Randomization) – therefore, patients taking an ACEI should have discontinued their ACEI medical therapy in the evening before Visit 2 (e.g. if Visit 2 is scheduled for Wednesday the last ACEI medication should be taken by the patient on Tuesday evening. The patient will then start to take the first dose of double blind study medication (sacubitril/valsartan or enalapril) on Thursday morning). If the patient continued to take their usual ACEI, the start of study drug has to be postponed to assure a ≥ 36 hours washout before first application of the study drug.

Patients taking an ARB should discontinue their ARB medical therapy the day of Visit 2 (e.g. if Visit 2 is scheduled for Wednesday the last ARB medication should be taken on Wednesday.

The patient will then start to take the first dose of double blind study medication (sacubitril/valsartan or enalapril) on Thursday morning).

Patients will start study treatment at dose level 2 (enalapril 5 mg bid or sacubitril/valsartan 49 mg/51 mg bid) unless the patients are suffering from moderate hepatic impairment, moderate renal impairment or patients with SBP ≥100 to 110 mmHg. These patients should be initiated at dose level 1, according to the the sacubitril/valsartan SmPC and the investigator's medical judgement (for these patients Visit 4B is neccessary). All patients must be stabilized on the chosen dose for 2 weeks.

At Visit 2, baseline IIEF-15, [redacted] and the sexual activity log need to be performed by the patients.

Visit 3 and 4

After 2 weeks of treatment (i.e. at Visit 3) the doses are up-titrated and after another 2 weeks (i.e. at Visit 4) all patients should have achieved the target dose of either 10 mg bid enalapril or 97 mg/103 mg bid sacubitril/valsartan, provided no safety and tolerability issues arise during up-titration. A blood draw for the safety lab needs to be performed 3-4 days prior to Visit 3 in order to have the results on the day of the visit to up-titrate the patient (for patients starting with dose level 1 an additonal safety lab is performed 3-4 days before Visit 4). The titration steps for the three dose levels are described in detail in **Section 5.5.3** (see **Table 5-1**). Every attempt should be made to keep the patients stable on dose level 3 in accordance with all safety parameters, which are symptomatic hypotension, renal dysfunction and/or hyperkalemia and should be handled according to the respective guidelines for management (see **Appendix 1**, **Appendix 2**, **Appendix 3**, **Appendix 4**, **Appendix 5** and **Appendix 6**). In case of lab deviations an unscheduled visit may be scheduled at the discretion of the investigator to re-assess lab parameters and evaluate the efficacy of taken measures. Measurements showing an elevation of potassium levels above the predefined values should be repeated and confirmed in a non-hemolyzed sample before any action is taken (for a serum potassium concentration greater than or equal to 6.0 mmol/L please refer to **Appendix 4**) .

For the following visits (no up-titration), a blood draw for lab assessments has to be done during the visit.

At Visit 3 and Visit 4, IIEF-15, a physical examination and the current NYHA status is documented, as well as safety monitoring and adverse events. At Visit 4, the questionnaires IIEF-15 [redacted] will be applied as well as a blood draw for the biomarker NT-proBNP.

Visit 4B – Optional

For patients achieving target dose at Visit 4, Visit 4B is needed to evaluate safety criteria and ensure adequate medical management. Investigator's clinical judgement and discretion is advised. For patients who started with dose level 1, this visit is mandatory.

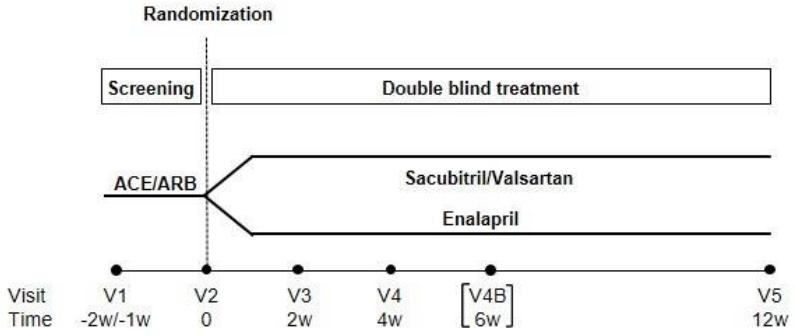
Visit 5 (End of Study)

After 3 months of treatment, a final assessment of patients is performed at Visit 5. IIEF-15 [redacted] questionnaires will be completed by patients at Visit 5. A blood draw for NT-proBNP assessment has to be done during the visit.

Unscheduled visits

In addition to the protocol-required visits, patients may be seen at any time throughout the study at the discretion of the investigator to follow any new lab abnormalities or AEs. All randomized patients, including any patient who has experienced a health event, should continue to receive double-blind treatment until the trial is completed, if possible in the opinion of the investigator. Unscheduled visits may also be performed throughout the study at the discretion of the investigator for up-titration of the study medication.

Figure 3-1 Study design



3.2 Rationale for study design

Sexual activity remains an essential aspect of QoL for patients with CHF. Unfortunately, erectile dysfunction is a common diagnosis in male patients with CHF constituting a substantial burden for the patients. Inhibition of neprilysin with sacubitrilat may enhance CNP levels in erectile tissue and contribute to maintaining an erection. It was already demonstrated that sacubitril/valsartan improved QoL in HFrEF patients including the intimate/sexual relationships section in a PARADIGM-HF post-hoc analysis (Chandra et al., 2018). Thus, the aim of the present study is to assess differences between sacubitril/valsartan versus enalapril in improving erectile function as assessed by the International Index of Erectile Function (IIEF-15) questionnaire in patients with HFrEF and ED. The questionnaire is established for assessing sexual function in ED patients and has been used in numerous clinical trials. For such a subjective endpoint as erectile function, a randomized, actively controlled, double-blind interventional trial with a balanced study population is the state of the art and allows controlling

the patients' treatment and thus reducing bias. Moreover, the study design is reasonable and adapted from recent studies for treatment of patients with CHF in terms of investigational treatment, duration of assessment period and the comparator. The study design is also in line with all required safety assessments and follow-ups for patients with CHF and for the treatment with sacubitril/valsartan and in compliance with the effective risk management plan for the product. Thus, events of angioedema, liver events, statin related events, and events of cognitive impairment are followed up by targeted questionnaires. Please refer to **Section 6.5** (safety assessments) for further details. Known risks of hypotension, renal impairment, and hyperkalemia are closely monitored to prevent severe events and are subject to separate guidance should such events occur. Please refer to **Sections 6.5.2** and **6.5.4** for assessments of blood pressure and laboratory assessments, respectively; and to **Appendix 1**, **Appendix 2**, **Appendix 3**, **Appendix 4** and **Appendix 5** for guidance to manage these risks.

Taken together, the present randomized, actively-controlled, double-blind, double-dummy approach is the most suitable design for achieving the study objective of demonstrating the superiority of sacubitril/valsartan versus enalapril in improving erectile function in patients with HFrEF and ED**Rationale for dose/regimen, route of administration and duration of treatment**

Strong clinical rationale for the target dose (97 mg/103 mg bid) as well as titration steps of sacubitril/valsartan is derived from the pivotal clinical trial PARADIGM-HF (McMurray et al., 2014) and this dosing schedule has been shown to be efficacious, safe (Senni et al., 2016) and is approved by the European Medicines Agency (EMA) for the treatment of symptomatic patients with chronic HF and reduced LVEF. The twice-daily dosing regimen of sacubitril/valsartan also ensures a sustained neprilysin (NEP) inhibition over 24 hours. The sacubitril/valsartan target dose of 97 mg/103 mg twice daily delivers a daily dose of valsartan equivalent to Diovan® 160 mg bid, the dose commonly recommended by current HF management guidelines (Ponikowski et al., 2016). With the purpose of this study to demonstrate the superiority of sacubitril/valsartan compared to enalapril in improving erectile function in patients with HFrEF and ED, we assume a measurable effect using the IIEF-15 questionnaire after 3 months of treatment.

3.4 Rationale for choice of comparator

Enalapril, the comparator chosen for this study, is an ACE inhibitor - the drug class considered first-line treatment by the current European therapy guidelines for the treatment of HFrEF patients (Ponikowski et al., 2016). ACE inhibitors and enalapril in particular, are the pharmacological standard of care for HFrEF management in Europe and – according to the current label – sacubitril/valsartan can be used to replace ACEI or ARBs in the management of HF. Since sacubitril/valsartan is tested in this study according to its label in treatment of patients with CHF, a standard-of-care comparator is thought to be most appropriate.
As a well-studied ACEI in HF, enalapril is used as the comparator in this study. Enalapril was studied in a number of previous large, outcome-driven studies, such as CONSENSUS (Group, 1987), SOLVD-Treatment (Investigators, 1991), and SOLVD-Prevention (Investigators et al., 1992).

Furthermore, in the pivotal clinical trial PARADIGM-HF (McMurray et al., 2014), enalapril was the active comparator for sacubitril/valsartan. Thus, enalapril was chosen as the active

comparator for the present study. Enalapril will be used in this study according to its label and recommended dosing of 10 mg bid, which is the most commonly recommended target dose for HFrEF patients and has been shown to reduce the risk of death and hospitalizations in HF patients (Investigators et al., 1992).

3.5 Purpose and timing of interim analyses/design adaptations

3.6 Risks and benefits

Both sacubitril/valsartan and enalapril are approved in the indication investigated within this study. Please refer to the corresponding Summary of Product Characteristics (SmPC) of each product as well as the Investigator's Brochure (IB) for sacubitril/valsartan for known adverse reactions, or special precautions on both IMPs (provided to all participating sites).

Patients will be instructed not to take any renin angiotensin aldosterone system (RAAS) blocking agents (ACEIs or ARBs) before start of study treatment in order to avoid excess RAAS blockade. **For ACEI a ≥ 36h washout period is mandatory**. The risk of temporary discontinuation of concomitant ACEIs or ARBs will be minimal as it will be reflective of the typical dosing schedule of most ACEIs and ARBs.

All patients will be allowed to continue receiving their other background CV medications.

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

If there is any question that the patient will not reliably comply, the patient should not be entered in the study. Participating patients will benefit from careful monitoring and follow-up during the entire study duration.

4. Population

This is an outpatient multi-center clinical study to be conducted in Germany. The goal is to randomize 200 patients in about 40 centers. Since a 30% screening failure rate is expected, approximately 286 patients will be screened. The study population will consist of a representative group of adult (≥18 and ≤ 75) male HFrEF patients in NYHA class II with mild to moderate ED. Eligible patients should be on a stable dose of an ACEI or an ARB as well as bisoprolol/metoprolol for at least 4 weeks prior to entering into the study.

The investigator must ensure that all patients who meet the inclusion criteria and do not fulfill any of the exclusion criteria are offered enrollment in the study. No additional parameter can be applied by the investigator.

4.1 Inclusion criteria

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

1. Patients must give written informed consent before any assessment is performed and must be willing and capable to comply with all study procedures
2. Male Outpatients ≥ 18 and ≤ 75 years of age

3. Patients with a diagnosis of CHF NYHA class II and reduced ejection fraction (< 40%) (assessed by any local measurement using echocardiography, CT scanning, MRI or ventricular angiography ≤ 6 months prior to Visit 1)
4. Plasma NT-proBNP level of ≥ 300 pg/mL at Visit 1
5. Patients must be living in a stable and sexually active heterosexual partnership for at least 6 months prior to Visit 1
6. Patients must have a mild to moderate erectile dysfunction determined using the IIEF-5 questionnaire (> 7 and ≤ 21 IIEF units) at Visit 1 and Visit 2
7. No usage of any available drug for erectile dysfunction (e.g. sildenafil, tadalafil) for at least 2 weeks prior to Visit 1 and 4 weeks prior to Visit 2
8. Patients must be on an ACEI or an ARB at a stable dose for at least 2 weeks prior to Visit 1 and 4 weeks prior to Visit 2
9. Patients must be treated with a stable dose of bisoprolol/metoprolol, unless the use of β-blockers is contraindicated or not tolerated (reason should be documented) for at least 2 weeks prior to Visit 1 and 4 weeks prior to Visit 2 (β-blockers other than bisoprolol/metoprolol are not allowed per protocol)
10. Patients must be literate in German

4.2 Exclusion criteria

Patients/subjects fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients/subjects.

1. Use of other investigational drugs during the study and within 30 days or 5 half-lives, whichever is longer before enrolment and at enrolment

2. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes, ACEIs, ARBs or NEP inhibitors, as well as known or suspected contraindications to the study drugs
3. Previous history of intolerance to recommended target doses of ACEIs or ARBs
4. Known history of angioedema
5. Requirement of treatment with a dual RAAS blockade, e.g. a treatment with both, ACEIs and ARBs or concomitant treatment with aliskiren
6. Current acute decompensated HF (exacerbation of chronic HF manifested by signs and symptoms that may require intravenous therapy)
7. Symptomatic hypotension and/or a systolic blood pressure (SBP) ≤100 mm Hg at Visit 1 (Screening) or Visit 2 (Randomization)
8. Estimated glomerular filtration rate (eGFR) < 30mL/min/1.73m^2 at Visit 1 (Screening) or Visit 2 (Randomization) as calculated by MDRD formula
9. Serum potassium level > 5.2mmol/L at Visit 1 (Screening) or Visit 2 (Randomization)
10. Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid or other major CV surgery, percutaneous coronary intervention (PCI) or carotid angioplasty within the 3 months prior to Visit 1
11. Coronary or carotid artery disease likely to require surgical or percutaneous intervention within the 3 months after Visit 1
12. Implantation of a pacemaker, implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy pacemaker / defibrillator (CRT-P/D), or upgrade of an existing device or revision of device leads within 3 months prior Visit 1 or intent to implant such a device during the study
13. Heart transplant or ventricular assistance device (VAD) or intent to transplant (on transplant list) or implant a VAD
14. History of severe pulmonary disease including COPD (Patients with significant chronic obstructive pulmonary disease contributing to dyspnea or patients whose COPD medication has been altered within 2 weeks prior to Visit 1 and 4 weeks prior to Visit 2)
15. Diagnosis of chemotherapy induced cardiomyopathy within the 12 months prior to Visit 1
16. Documented untreated ventricular arrhythmia with syncopal episodes within the 3 months prior to Visit 1
17. Known symptomatic bradycardia or second or third degree heart block without a pacemaker
18. Known presence of hemodynamically significant mitral and/or aortic valve disease, except mitral regurgitation due to left ventricular dilatation
19. Presence of other hemodynamically significant obstructive lesions of left ventricular outflow tract, including aortic and sub-aortic stenosis
20. Known history of familial long QT syndrome or known family history of Torsades de Pointes
21. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs, including but not limited to any of the following:
    - AST or ALT values exceeding 2 x upper limit of normal (ULN)

- History of active inflammatory bowel disease during the 12 months before Visit 1
- Current duodenal or gastric ulcers during the 3 months prior to Visit 1
- Gastric bypass
- Evidence of severe hepatic impairment, biliary cirrhosis or cholestasis, classified as Child-Pugh C
- History of hepatic encephalopathy, history of esophageal varices, history of portocaval shunt
- Active treatment with bile sequestering agents such as cholestyramine or colestipol resins

22. Presence of any other disease with a life expectancy of < 1 years
23. Presence of known bilateral renal artery stenosis
24. Penile anatomical defects and Peyronie's disease
25. Foreseeable usage of any available drug for erectile dysfunction (e.g. sildenafil, tadalafil) during the study
26. Co-Medication with an influence on erectile function such as digoxin, anticholinergic anti-depressants, alpha blockers finasteride and calcium channel blockers
27. Recent (4 weeks prior to Visit 1) or planned (within the 14 weeks after Visit 1) change in statin or spironolactone therapy
28. Diabetes mellitus Type I or insulin-dependent Type II
29. Prostate-specific antigen (PSA) levels higher than 4 ng/mL at Visit 1 or known prostate cancer
30. Spinal cord injury, ileostomy, prior surgery or radio therapy for rectal or prostate cancer and radical prostatectomy
31. Presence of peripheral artery occlusive disease and/or stenosis of the common and internal iliac artery
32. Patients with ongoing alcohol and/or drug abuse and/or severe depression (defined as patients with altered medication or hospitalization within 4 weeks prior to Visit 1 and Visit 2)
33. Presence and suspicion of any neurodegenerative disease or polyneuropathy
34. Hormonal abnormalities such as hypogonadism, hyperprolactinemia, hyper- and hypocortisolism and medically untreated hyper- and hypothyroidism
35. Obesity based on a body mass index $\geq$35 kg/m^2, frail patients or patients with cardiac cachexia or a body mass index <18.5 kg/m^2
36. Any surgical or medical condition, which in the opinion of the investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study.

5. Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Double blind treatment

All eligible patients will be randomized in a 1:1 allocation to receive either sacubitril/valsartan or enalapril in addition to optimal CHF therapy, as considered appropriate by the investigator and in accordance with standard therapy guidelines, but with the exception of an ACEI or ARB, as this will be replaced by investigational treatment at Visit 2 (Randomization). The use of an ACEI or an ARB in addition to investigational treatment is **strictly prohibited.** For ACEIs a washout period of ≥ 36 hour is mandatory. During the dosing of study medication, i.e. beyond randomization until the end of the study, the intake of ACEIs or ARBs remains prohibited (in case of treatment interruption/discontinuation see **Section 5.5.5** and **Section 5.5.6**).

The following study drugs will be provided:

- Sacubitril/valsartan 24 mg/26 mg film-coated tablets (sacubitril/valsartan dose level 1)
- Placebo to match sacubitril/valsartan 24 mg/26 mg film-coated tablets (placebo matching sacubitril/valsartan dose level 1)
- Sacubitril/valsartan 49 mg/51 mg bid film-coated tablets (sacubitril/valsartan dose level 2)
- Placebo to match sacubitril/valsartan 49 mg/51 mg bid film-coated tablets (placebo matching sacubitril/valsartan dose level 2)
- Sacubitril/valsartan 97 mg/103 mg film-coated tablets (sacubitril/valsartan dose level 3)
- Placebo to match sacubitril/valsartan 97 mg/103 mg film-coated tablets (placebo matching sacubitril/valsartan dose level 3)
- Enalapril 2.5 mg film-coated tablets (enalapril dose level 1)
- Placebo to match enalapril 2.5 mg tablets (placebo matching enalapril dose level 1)
- Enalapril 5 mg film-coated tablets (enalapril dose level 2)
- Placebo to match enalapril 5 mg tablets (placebo matching enalapril dose level 2)
- Enalapril 10 mg film-coated tablets (enalapril dose level 3)
- Placebo to match enalapril 10 mg tablets (placebo matching enalapril dose level 3)

Target doses: Sacubitril/valsartan 97 mg/103 mg bid and enalapril 10 mg bid

All tablets have different shapes and colors. Therefore, the study will be designed as a double-blind, double-dummy trial to ensure the blinding during the entire course of the study. To maintain the blinding, patients will be required to take their assigned active treatment tablet along with placebo matching the opposite treatment twice daily (morning and evening dose) in addition to their conventional concomitant therapy.

Sacubitril/valsartan and its matching placebo will be provided in HDPE bottles and/or blister packs. Enalapril and its matching placebo will be provided in HDPE bottles and/or blister packs.

5.1.2 Additional treatment

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

5.2 Treatment arms

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

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

5.3 Treatment assignment and randomization

5.4 Treatment blinding

5.5 Treating the patient

5.5.1 Patient numbering

5.5.2 Dispensing the study drug

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

5.5.3.2 Handling of additional treatment

5.5.4 Instructions for prescribing and taking study treatment

Patients will be provided with medication packs containing the study drug corresponding to their assigned treatment arm and dose level, sufficient to last until their next scheduled visit. In order to maintain blinding, patients will be required to take two tablets (one sacubitril/valsartan or its matching placebo and one enalapril or its matching placebo) twice a day for the duration of the study. **Table 5.1** summarizes the study drug that will be taken during the double-blind period.

Patients will begin treatment with dose level 2 for 2 weeks. At Visit 3, patients will be up-titrated to dose level 3 unless safety monitoring criteria prevent up-titration. According to the sacubitril/valsartan SmPC and the investigator's medical judgement, patients suffering from moderate hepatic impairment (Child Pugh B), moderate renal impairment or patients with SBP ≥100 to 110 mmHg should be initiated at dose level 1. They will be up-titrated every 2 weeks (unless safety monitoring criteria prevent up-titration) until they reach dose level 3. Visit 4B is

a mandatory visit for patients achieving target dose (dose level 3) at visit 4 to evaluate safety criteria and ensure adequate medical management.

Table 5-1 Study drug dispensed during the double-blind period

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

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

Patients will be instructed to take their morning study drug doses at approximately 08:00 (8 AM) and their evening study drug doses at approximately 19:00 (7 PM). The study medications should be taken with a glass of water with or without food. If the patient misses taking any study drug dose, he should take it as soon as possible, unless if it is almost time for the following scheduled dose. In this case, the patient should skip the missed dose and return back to his regular study drug administration schedule.

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

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

5.5.5 Permitted dose adjustments and interruptions of study treatment

Once patients achieve the target study drug dose, every attempt should be made to maintain the target study drug dose level (dose level 3) for as long as possible throughout the trial. If, however, in the opinion of the investigator, the patient does not tolerate the target dose of the study drug, the investigator should consider whether non-disease modifying medication (e.g. diuretics, nitrates) can be reduced to rectify the situation, before considering to reduce the dose of study drug to the next lower dose level. In addition, the investigator may adjust the doses of disease -modifying medications, if he/she believes that they are more likely causes of adverse events. If such adjustments of concomitant medications are not medically indicated, the investigator may down-titrate the dose of study drug to the next lower dose level up to a complete withdrawal of the investigational treatment, if necessary. In such cases, the patient should be re-challenged with the higher dose when the investigator feels that doing so is appropriate; the re-challenge should be performed according to the guidance provided in this section (see below) of the protocol.

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

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

- Hyperkalemia (see **Appendix 4**)
- Symptomatic hypotension (see **Appendix 5**)
- Clinically significant decrease in eGFR or clinically significant increase in serum Creatinine (see **Appendix 6**)
- Worsening hepatic function (see **Appendix 2**)

After randomization, temporary study drug discontinuation for any reason does not automatically constitute withdrawal from the study and should not lead to the patient being withdrawn from the study.

Adjustment of study drug dose level

If despite adjustment of concomitant medications per the guidance provided above the situation is not rectified, the investigator may consider adjusting the study medication according the following instructions.

During the double-blind treatment period down-titration of the study drug at any time will be allowed based on the safety and tolerability criteria defined in **Appendix 1**, **Appendix 2**, **Appendix 3**, and **Appendix 4**. If down-titration is necessary, the patient should be down titrated to the next dose level (see **Table 5-1**). The patient may continue receiving the lower dose level for a recommended period of 1 to 2 weeks before re-challenging the patient with the next higher dose level. For example, a patient who encounters tolerability problems at the target dose level (dose level 3), should receive the study drug at dose level 2 for 1 to 2 weeks. Then, he should be re-challenged with up-titration back to dose level 3.

If the tolerability issues are not alleviated, the investigator may lower the study drug dose further to the next lower level for 1 to 2 weeks, up to temporary withdrawal of the study drug. Again, once stable, the patient should be re-challenged with up-titration to the next higher dose level every 1 to 2 weeks in an attempt to bring back the patient gradually to the target study drug dose level (dose level 3). The investigator may choose the next dose level for down- or up-titration according to his or her judgment (**Table 5-1**).

In some cases, according to the safety and tolerability criteria and the investigator's judgment, dose level 1 or 2 could be maintained if he/she considers that the patient's condition would not allow an up-titration to the target dose of study medication (level 3). In this case, it would be acceptable to maintain the patient at dose level 2 (or lower), to assure treatment with the highest dose level tolerated by the patient.

Study drug restart after temporary treatment interruption

Study drug should be reintroduced after 1-2 weeks in those who temporarily discontinue as soon as medically justified in the opinion of the investigator.

Once the investigator considers the patient's condition appropriate for receiving the study drug, the investigator should re-start the patient on the study drug at the most appropriate and

allowable dose level (**Table 5-1**) per his/her medical judgment. If tolerated based on the safety and tolerability criteria in **Appendix 1**, **Appendix 2**, **Appendix 3**, and **Appendix 4** the patient should be up-titrated to the next dose level (up to dose level 3) every 1 to 2 weeks, as per the investigator's judgment.
Patients re-started on the study drug will retain their original randomization and study identification numbers. Should the patient not tolerate the re-start study drug dose level, he may be down-titrated again (if appropriate) or discontinue the study medication. Up-titration or reintroducing the study drug could be considered by the investigator as soon as medically justified in his/her medical judgment.
Study visits should occur as close as possible to the time points indicated in **Table 6-1**. The timeframe between the regular visits should be maintained as scheduled, irrespective of the number of unscheduled visits that may be performed in between, according to the visit and time schedule described in **Table 6-1**.

Any changes in the study drug dose level, including temporary/permanent withdrawal or re-start of the study drug, must be recorded on the Dosage Administration Record CRF.

5.5.6 Rescue medication

Guidance on handling hyperkalemia, hypotension and renal dysfunction are provided in **Appendix 1**, **Appendix 4**, **Appendix 5** and **Appendix 6**. If necessary, patients may receive open-label ACEI and/or ARBs **ONLY** if study medication is interrupted temporarily or discontinued permanently. NOTE that a washout phase of ≥ 36 hours is required for the study drug (in case the patient is switched to an ACEI), but also for any ACEI before (re-)introducing study drug.

Use of rescue medication must be recorded on the appropriate CRF.

5.5.7 Concomitant medication

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

ACEIs and ARBS

The patients' pre-study ACEIs or ARBs will be replaced by the study drug. As per inclusion criteria, the patients need to be on stable HF therapy regimen for at least 4 weeks prior to Visit 2 and should remain on a stable regimen, if medically justified, throughout the entire study duration.

The concomitant use of open-label ACEIs or ARBs is strictly prohibited while the patient is receiving study medication. If the investigator believes that addition of an ACEI or ARB is

necessary, then study drug must be discontinued. Study medication should be stopped ≥ 36 hours prior to addition of **open-label ACEI**. If not already treated with an aldosterone antagonist, consideration should be given to adding this therapy rather than an ACEI or ARB.

Similarly, if study medication is to be restarted, the open-label **ACEI should be discontinued ≥ 36 hours prior to resuming study medication**.

Phosphodiesterase-5 (PDE-5) inhibitors

The use of Phoshodiesterase-5 inhibitors (e.g. sildenafil, vardenafil, tadalafil and compounds with similar characteristics) **is not allowed during the study**.

However, there is a risk that patients make use of PDE5i, despite being not allowed by the study protocol. For this reason, investigators are advised to make all efforts to make the patient aware that use of PDE5i is not allowed. The investigator should educate the patient concerning the increased possibility of the occurrence of hypotension.

Statins

Caution should be exercised upon co-administration of statins such as atorvastatin, simvastatin, pravastatin and/or pitavastatin and study medication, due to potential interactions between statins and sacubitril/valsartan.

Other drugs with a potential impact on erectile function

The treatment with the following medications with a potential influence on erectile function are not allowed:

- **Digitoxin, Digoxin** (e.g. Digacin, Lanicor, Lenoxin and compounds with similar characteristics)
- **Calcium channel blockers** (e.g. Verapamil, Gallopamil, Diltiazem, Amlodipin, Nitrendipin, Felodipin, Nidedipin and compounds with similar characteristics)
- **Alpha blockers** (e.g. Alfuzosin, Tamsulosin, Doxazosin, Phentolamin, Prazosin, Uradipil, Ergotamin and compounds with similar characteristics)
- **Anticholinergic anti-depressants** (e.g. amitriptyline, doxepin and compounds with similar characteristics)
- **Finasteride**

Potential interactions between sacubitril/valsartan and lithium or non-steroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase-2 (COX-2) inhibitors should be considered.

Due to potential drug interactions between ACE-inhibitors and specific anti-diabetic medication (such as insulins, specific oral hypoglycemic agents) as well as potential interaction between metformin and sacubitril/valsartan, patients on antidiabetic treatment are encouraged to be

followed up to ensure adequate management of their diabetes according to investigators discretion.

Medications known to raise potassium levels

Potassium-sparing diuretics, potassium supplements, aldosterone antagonists, and any other medications known to raise potassium levels should be used with caution while the patient is receiving the study medication due to the increased possibility of occurrence of hyperkalemia. The investigator is encouraged to assess patients' potassium levels regularly, especially in those who are receiving these medications. Guidelines for the management of hyperkalemia can be found in **Appendix 4**.

5.5.8 Prohibited medication

Use of the treatments displayed in the **Table 5-2** is NOT allowed after the start of the investigational drug. For ACEI a washout period of ≥ 36 hours is mandatory.

In order to avoid excessive RAAS inhibition, it is crucial to respect the washout period and instruct the patient to not take any ACEI or ARB while taking double-blind study medication.

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

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

β-blockers other than bisoprolol/metoprolol are not allowed per protocol due to interference with erectile function.

Table 5-2 Prohibited medication

Medication	Prohibition period	Action taken
Any ACEI, ARB or Renin inhibitors	Double blind period (≥ 36h washout period for ACEI)	Prohibited until at least 36 hours after study drug discontinuation/interruption/end of study (for ACEI). In case these drugs are taken / need to be taken during the double-blind treatment period of the study, discontinue study drug
PDE5i	Double blind period	Discontinue before randomization, prohibited throughout the study. No action required with study medication

Medication	Prohibition period	Action taken
Bile acid sequestering agents (e.g. Cholestyramine, Colestipol)	Double blind period	Discontinue before randomization, prohibited throughout the study. No action required with study medication
Calcium channel blockers (e.g. Verapamil, Amlodipin)	Double blind period	Discontinue before randomization, prohibited throughout the study. No action required with study medication
Alpha blockers (e.g. Tamsulozin, Prazosin, Ergotamin)	Double blind period	Discontinue before randomization, prohibited throughout the study. No action required with study medication
Anticholinergic anti-depressants (e.g. Amitryptiline, Doxepin)	Double blind period	Discontinue before randomization, prohibited throughout the study. No action required with study medication
Digitoxin	Double blind period	Discontinue before randomization, prohibited throughout the study. No action required with study medication
Digoxin (e.g. Digacin, Lanicor)	Double blind period	Discontinue before randomization, prohibited throughout the study. No action required with study medication
β-blockers other than bisoprolol/metoprolol	Double blind period	Prohibited throughout the study. No action required with study medication
Finasteride	Double blind period	Discontinue before randomization, prohibited throughout the study. No action required with study medication

5.5.9 Emergency breaking of assigned treatment code

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

5.6.2 Discontinuation of study treatment

- Suspected occurrence of angioedema. A patient with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the investigator and constitute a reason for temporary or permanent discontinuation of study treatmentUse of prohibited treatment as per **Table 5-2**. In case of initiation of open-label ACEI during the double blind treatment period, study medication must be stopped for ≥36 hours prior to initiation of open-label ACEI. The open label ACEI must be stopped for ≥36 hours prior to re-initiation of study drugDepending on the serum potassium, blood pressure, or eGFR, patients may need to have their study drug dose or the dose of another concomitant medication reduced or discontinued, or, if appropriate, have potentially contributing agents adjusted. Please refer to **Appendix 4**, **Appendix 5**, and **Appendix 6** for treatment guidelines for hyperkalemia, hypotension, or renal dysfunction, respectively.**Withdrawal of informed consent**

5.6.4 Loss to follow-up

5.6.5 Early study termination by the sponsor

6. Visit schedule and assessments

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

Patients/subjects must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

Table 6-1 Assessment schedule

Visit	**1**	**2**	**3**	**4**	**4B**	**5**	**TD and/or PSD**	
Time	**-2w to -1w**	**0**	**2w**	**4w**	**6w**	**12w**		
Obtain informed consent	X							
Inclusion/Exclusion criteria	X	X						Some exclusion criteria apply for both Visit 1 and Visit 2
Demography	X							
Medical History	X	X[1]						
NYHA Classification	X	X	X	X	(X)	X	X	
Previous and concomitant drug/non-drug treatments	X	X	X	X	(X)	X	X	
Physical Exam	X	X	S	S	(S)	X	S	At Visit 1 (Screening), 2 (Randomization), and 5 (EOS) a full physical exam is performed; at all other visits a short exam is to be performed (see Section 6.5.1)
Height	X							
Weight	X					X	X	
Vital signs	X					X	X	
IIEF-15		X	X	X		X	X	
IIEF-5	X	X						
Dispense Sexual Activity Log		X						
Sexual Activity Log		X	X[4]	X[4]	X[4]	X[4]	X	Sexual activity Log is completed by the patient once a week. Baseline value is assessed at Visit 2
[redacted]								
Diagnostic and Laboratory evaluations	X[2]	X[3]		X		X	X	Hematology and Biochemistry
NT-proBNP	X	X[3]		X		X	X	
Laboratory assessment			X[3]	(X[3,5])	(X)			Abbreviated assessment for Potassium, AST and ALT and Creatinine/eGFR.
Dispense Study Medication		X	X	X				

Visit	**1**	**2**	**3**	**4**	**4B**	**5**	**TD and/or PSD**	
Time	**-2w to -1w**	**0**	**2w**	**4w**	**6w**	**12w**		
Drug accountability			X	X	(X)	X	X	
Adverse event monitoring	X	X	X	X	(X)	X	X	
Contact IVRS/IWRS	S	S	S	S	(S)	S	S	
Study Completion form							X	

TD = Study treatment discontinuation; PSD = Premature subject/patient discontinuation
X = assessment to be recorded on clinical data base
S = assessment to be recorded on source documentation only
"( )" = Assessments for Visit 4B are in brackets, as Visit 4B is a visit not applying to all patients
IIEF = International Index of Erectile Function
[redacted]
[1] = Medical history as far as needed for inclusion and exclusion criteria
[2] = PSA level will be determined at Visit 1
[3] = Blood draw 3-4 days before Study Visit (central lab)
[4] = sexual activity log is completed once a week by the patient
[5] = The laboratory assessment (safety lab) only applies for patients who started with dose level 1 (Cave: these patients need to come 3-4 days before Visit 4 for the blood draw). The Diagnostic and Laboratory Evaluations at Visit 4 are performed at the regular visit.

6.1 Information to be collected on screening failures

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: year of birth, age, sex, race, source of patient referral (if applicable), the patients' living conditions, smoking status, relevant medical history/current medical condition present before signing informed consent (where possible, diagnoses and not symptoms will be recorded) previous drug/non-drug therapy of HF (prior Visit 1 and 2), concomitant medication and non-drug therapy. Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.3 Treatment exposure and compliance

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.4 Efficacy

- Patient-reported frequency of sexual activity
- NT-proBNP
- [redacted]

6.4.1 IIEF-15 questionnaire The International Index of Erectile Function (IIEF-15) is a patient self-reported questionnaire to assess ED in male patients (see annex for detailed information). It consists of 15 questions assessing five main principles associated with ED: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. For each question, 0-5 points can be achieved with 5 being the best outcome (Rosen et al., 1997). In this study, the IIEF-15 will be completed by patients at baseline (Visit 2), as well as at 2 weeks (Visit 3), at 1 month (Visit 4) and at 3 months (Visit 5) and all categories will be evaluated separately: erectile function (questions 1-5; 15), orgasmic function (questions 9-10), sexual desire (questions 11-12), intercourse satisfaction (questions 6-8) and overall satisfaction (questions 13-14).

6.4.2 Patient-reported frequency of sexual activity

Since the quantitative amount of sexual activity is not covered in the IIEF-15, patients will keep a diary to log any sexual activity during the whole study period starting with an initial assessment at Visit 2 covering sexual activity the week before Visit 2. This self-assessment will be completed by the patients on an electronic device (tablet). Patients are asked to complete the diary once per week until end of the study (Visit 5). The diary consists of seven items assessing the patients' sexual activity of the previous 7 days.

6.4.3 NT-proBNP

Plasma NT-proBNP will be obtained in all patients by using the central laboratory at Visit 1 to determine eligibility for participation in the trial. In addition, plasma NT-proBNP is assessed at Visit 2, 4 and 5.

[redacted]

Appropriateness of efficacy assessments

IIEF-15

The International Index of Erectile Function Questionnaire (IEF-15) is a validated, multi-dimensional, self-administered 15-item questionnaire for the assessment of erectile function. The IIEF was developed and validated in the 1990s and used in various clinical trials (Rosen et al., 1997, Wiltink et al., 2003).

Therefore, the IIEF-15 is an appropriate tool to measure erectile function in clinical trials.

[redacted]

Patient-reported sexual activity

Although the IIEF-15 questionnaire is assessing erectile function, it is not measuring sexual activity other than intercourse with vaginal penetration, or the attempt to vaginal intercourse. However, sexual activity can also include sexual actions like masturbation, sexual foreplay or intimacy with a partner. Sexual activity other than intercourse is also an important part of Quality of Life (McCabe, 1997). Therefore, a sexual activity diary was developed to assess the patients' sexual activity and QoL associated with the patients'sexual activity.

NT-proBNP

NT-proBNP is a biomarker relevant to the pathophysiology of cardiovascular disease and has shown prognostic value in large clinical trials. Therefore, NT-proBNP is an appropriate readout for the progression of cHF (Zile et al., 2016, McMurray et al., 2014).

6.5 Safety

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

6.5.2 Vital signs

Vital signs include BP and pulse measurements. BP will be measured by using a standard sphygmomanometer with an appropriate size cuff and the non-dominant arm in the sitting position after 5 minutes of rest.

Guidelines for the management of BP are provided in **Appendix 5**.**Height and weight**

6.5.4 Laboratory evaluations

The investigator or his/her designee should review the central laboratory results as soon as they become available to decide on whether any adjustments in the patient's study drug or non-study drug regimen are needed. Therefore, unscheduled visits are possible based on investigator's discretion.

All central laboratory results will be communicated to the investigators and the sponsor. Details on the collection, shipment of samples and reporting of results by the central laboratory will be provided to investigators in the laboratory manual.

Laboratory values that exceed the boundaries of a notable laboratory abnormality must be commented on by the investigator in the Comments screen of the patient's eCRF and additional laboratory evaluations should be performed, as judged appropriate by the investigator. If the laboratory abnormality induces clinical signs or symptoms, or requires therapeutic intervention, then the diagnosis or medical condition must be entered on the AEs screen of the patient's eCRF. If the laboratory abnormality is the primary reason for an unforeseen hospitalization or otherwise fulfills the seriousness category of an AE, then the procedure for rapid notification of SAEs must be followed. Likewise, if the laboratory abnormality leads to discontinuation from the study drug (temporarily or permanently), the patient must be followed until the abnormality resolves or until it is judged to be permanent.

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential counts, and platelet count will be measured at Visits 1, 2, 4, 5 and in case of study treatment discontinuation (TD) or premature subject/patient discontinuation (PSD).**Clinical chemistry**

Glucose, blood urea nitrogen (BUN), Blood urea, creatinine, creatinine kinase, total bilirubin, AST, ALT, alkaline phosphatase, INR, GFR, HbA1c absolute, HbA1c relative, sodium, potassium, chloride, calcium, total protein, albumin, HDL, LDL, triglycerides, and uric acid will be measured at visits 1, 2, 4, 5 and in case of TD or PSD.

BUN, creatinine, GFR, potassium and urea will be obtained from patients at every visit when a complete laboratory test is not done (i.e., Visit 3, 4 and 4B, please see **Table 6-1** for details).

The latter is true for all unscheduled visits done with up-titration intention.**Urine analysis**

6.5.5 Electrocardiogram (ECG)

6.5.6 Pregnancy and assessments of fertility

6.5.7 Angioedema

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

It is important that the investigator pays special attention to any swelling or edema that may resemble angioedema or angioedema-like events that may be reported by patients. If such an event occurs, the investigator will complete an Adjudication Questionnaire for an Angioedema-like Event form (provided by Novartis) to summarize the event, its treatment, and its ultimate outcome. This report along with the requisite medical documentation must be submitted to Novartis as soon as possible. Follow-up reports must be communicated to Novartis as soon as new information regarding the event becomes available. All hospital records related to the event must be communicated to Novartis. The investigator may be also be contacted by Novartis regarding AEs that may resemble an angioedema-like event. A list of terms that are considered "angioedema-like" (e.g., periorbital swelling) will be provided to sites in a manual. The investigator or his/her delegated staff must complete the required forms and provide the required medical records for all such events, regardless of whether the investigator views the event in question as angioedema or not.

All angioedema reports will be forwarded to an Angioedema Adjudication Committee by Novartis for assessment. Information regarding this committee is outlined in Section 8.5. Details on the procedures for reporting angioedema events will be provided to investigators in a manual.

6.5.8 Cognitive Impairment

Angiotensin receptor blockade has been suggested to improve cognitive function, as might overall improvement in cardiac and vascular function. Thus, improvements in cardiac function and cerebral blood flow by LCZ696 are hypothesized to potentially improve vascular effects and, thereby, cognition. However, neprilysin is one of multiple enzymes involved in the breakdown of amyloid β, a peptide linked to cognitive impairment. Thus, cognitive function resulting from combined angiotensin receptor blockade and neprilysin inhibition with LCZ696 is subject to standardized follow-up.

It is important that the investigator pays attention to any events of cognitive impairment or related events that may be reported by patients. If such an event occurs that meets criteria for serious adverse event, the investigator will complete a separate questionnaire for a Dementia-related Event form (provided by Novartis) to summarize the event, its further diagnostic tests

performed, and its related information. A list of terms that are considered "dementia-like" (e.g., presenile dementia, memory impairment) will be provided to sites in a manual.

6.5.9 Statin-related Events

Statin-related events are subject to additional safety assessments and thus are followed with a standardized questionnaire. A list of terms that are considered "statin-related" (e.g., rhabdomyolysis, acute pancreatitis, myalgia and muscle spasm) will be provided to sites in a manual.

If such an event occurs that meets criteria for serious adverse event, the investigator will complete a separate questionnaire for a Hepatotoxicity and Statin-related Event form (provided by Novartis) to summarize the event, its further diagnostic tests performed, and its related information.

6.5.10 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.**Other assessments**

6.6.1 Patient Reported Outcomes (PRO)

6.6.2 Pharmacokinetics

6.6.3 Other biomarkers

7. Safety monitoring

7.1 Adverse events

The FAS will be the patient population for the above analyses.**Treatments**

The FAS will be used for the above analyses.**Analysis of the primary variable(s)**

9.4.1 Primary Variable(s)

The primary endpoint is the Erectile function score IIEF-15 at 3 months. The trial aims to estimate the effect of the treatment policy, irrespective of intercurrent events such as dose changes or adherence to randomized treatment. The following estimand will be used:

- Population – Full Analysis Set (FAS)

- Variable of Interest – Erectile function score IIEF-15 at 3 months
- Intervention effect – effect between sacubitril/valsartan versus enalapril at 3 months regardless of adherence to randomized treatment.
- Summary measure –difference in means

For patients who permanently discontinue study treatment, values collected after study drug discontinuation will generally be included in the analysis.

9.4.2 Statistical model, hypothesis, and method of analysis

The primary variable will be analyzed using a mixed model for repeated measures (MMRM), The response variable will be the Erectile function score IIEF-15. Treatment (sacubitril/valsartan versus enalapril), visit and treatment-by-visit interaction will be included as fixed-effect factors; baseline IIEF-15 will be included as a covariate; the within-patient covariance will be modeled using an unstructured covariance matrix (a common matrix for the two treatment groups). The analysis will include all (two) scheduled post-baseline visits and will be performed based on the likelihood method with an assumption of missing at random (MAR) for missing data.

The null-hypothesis to be rejected is that there is no difference in mean IIEF-15 scores at 3 months between the two treatment arms, in mathematical terms: H_0: $\mu_1 = \mu_2$ vs. H_a: $\mu_1 \neq \mu_2$, where μ_1 and μ_2 are mean IIEF-15 scores at 3 months for the treatment groups of sacubitril/valsartan versus enalapril, respectively.

The statistical test will be performed at the two-sided significance level of 0.05 based on the MMRM model. The estimates and the corresponding 95% confidence intervals will be provided for the difference in adjusted means at month 3 between the two treatment groups based on the MMRM model. Although this test is defined as two-sided, superiority of sacubitril/valsartan versus enalapril will be claimed only, if the difference is in favor of sacubitril/valsartan.

The FAS will be used for the above primary analyses.

9.4.3 Handling of missing values/censoring/discontinuations

Patients will be followed up and all scheduled visits should be performed, even if study drug is discontinued for that respective patient prematurely. Therefore, missing values should only occur in case of death, withdrawal of informed consent or loss to follow up. In these cases, patients will be included with their available values into the statistical MMRM model.

9.4.4 Sensitivity analyses

The following estimand will be used:

- Population – Full Analysis Set (FAS)
- Variable of Interest – Erectile function score IIEF-15 at last observed visit
- Intervention effect – effect between sacubitril/valsartan versus enalapril at last observed visit regardless of adherence to randomized treatment.

- Summary measure – difference in means

For patients for whom an IIEF-15 at month 3 is available, this value will be used, regardless of adherence to treatment. Analysis will be performed using an Analysis of Covariance model for IIEF-15 at last observed visit with factor treatment group and covariate baseline IIEF-15.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

9.5.2 Safety variables

Safety assessments will be based mainly on the frequency of adverse events. Adverse events will be coded by primary system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). An adverse event related to study drug is defined as one considered by the investigator to have a suspected relationship with the study drug. The adverse events will be summarized by the number and percentage of patients in each primary system organ class and preferred term. For summaries by severity of event, the most severe occurrence for a particular preferred term will be used for a given patient. Summary tables of adverse events by treatment and severity will be provided.

Multiple occurrences of the same AE or SAE in the same patient will be counted only once, using the worst severity and drug relationship.

In the data listings of adverse events, the severity of an AE, whether or not an AE is study drug related, and whether or not it is a serious AE, will be indicated.

Laboratory data will be summarized by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges) and by presenting number and percentage of patients with notable laboratory abnormalities according to **Appendix 1**.

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

9.5.3 Resource utilization

9.5.4 Pharmacokinetics

9.5.5 DNA

9.5.6 Biomarkers

9.5.7 PK/PD

[redacted]

[redacted] **Interim analyses**

Not applicable, no interim analysis will be performed.

9.8 Sample size calculation

For the IIEF-15 domain "erectile function", the treatment effect and SD of sacubitril/valsartan compared to enalapril was estimated based on the previous VALED study, which demonstrated that valsartan showed a highly significant increase in erectile function from 16.54±8.27 to 23.14±6.49 IIEF units in hypertensive males (Dusing, 2003). VALED was an open-label study comparing 6 months treatment with valsartan to baseline. CONFIDENCE on the other hand is a double-blind randomized trial and the beneficial effect of sacubitril/valsartan will likely be driven not by valsartan but by the neprilysin inhibition introduced by sacubitril. For sample size calculation the shorter study period, differing patient population (heart failure versus hypertension) as well as the use of bisoprolol/metoprolol have to be taken into account. Beta-blocker have differing effects on erectile function. While propranolol and atenolol are well-known to reduce sexual function, nebivolol has vasodilating effects, which may even be beneficial in erectile dysfuntion (Baumhakel et al., 2011). Bisoprolol/metoprolol have been suggested to have a neutral effect on erectile dysfunction (Baumhakel et al., 2011) and were thus chosen as the allowed concomitant beta-blockers within the study.

Therefore, a treatment effect of sacubitril/valsartan compared to enalapril of 3.5 IIED units was estimated. Assuming a standard deviation of 7 IIEF units and a two-sided alpha of 0.05, 86 patients per arm would confer a 90% power to detect a conservative treatment difference of 3.5 IIEF units. This is in accordance with the minimal clinically important difference of the erectile function domain of IIEF-15 of 2 and 5 IIEF units in patients with mild and moderate erectile dysfunction, respectively (Rosen et al., 2011).

To compensate for some drop-out and other protocol deviations, 100 patients/arm (200 in total) should be randomized into this trial. There will be no additional recruitment in case some patients will not be able to achieve the target dose since based on PARADIGM-HF and a shorter trial duration, no substantial influence on the power of the trial is expected.

10. Ethical considerations

10.1 Regulatory and ethical compliance

10.2 Informed consent procedures

10.3 Responsibilities of the investigator and IRB/IEC

10.4 Publication of study protocol and results

10.5 Quality Control and Quality Assurance

11. Protocol adherence

11.1 Protocol amendments

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13. Appendix 1: Clinically notable laboratory values

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

Hematology	
RBC count	>50% increase, >20% decrease
Hemoglobin	>50% increase, >20% decrease
Hematocrit	>50% increase, >20% decrease
WBC count	>50% increase, >50% decrease
Platelet count	>75% increase, >50% decrease
Blood Chemistry	
ALT (SGPT)	>150% increase
AST (SGOT)	>150% increase
BUN	>50% increase
Creatinine	>50% increase
Total bilirubin	>100% increase
CPK	>300% increase
Alkaline phosphatase	>100% increase
Potassium	>20% increase, >20% decrease
Chloride	>10% increase, >10% decrease
Calcium	>10% increase, >10% decrease
Uric acid	>50% increase

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

Table 14-1 Liver Event and Laboratory Trigger Definitions

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

15. Appendix 3: Specific Renal Alert Criteria and Actions

Table 15-1 Specific Renal Alert Criteria and Actions

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

General principles

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

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

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

Corrective action for management of hyperkalemia

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

- Confirm potassium concentration in a non-hemolyzed sample
- Reinforce low potassium diet and restriction of food/drinks with high potassium content (e.g. orange juice, melon, bananas, low-salt substitutes etc.)
- Review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia. Consider reduction in dose or discontinuation of these agents:
- Aldosterone antagonists (if they are believed to be the most likely cause of hyperkalemia)
- Potassium-sparing diuretics (e.g. amiloride and triamterene) including in combination products with thiazide or loop diuretics
- Potassium supplements, e.g., potassium chloride
- Salt substitutes
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Cyclo-oxygenase-2 (COX-2) inhibitors

- Trimethoprim and trimethoprim-containing combination products, such as trimethoprim/sulfamethoxazole fixed combinations
- Herbal Supplements: For example, Noni juice, alfalfa (Medicago sativa), dandelion (Taraxacum officinale), horsetail (Equisetum arvense), nettle (Urtica dioica), milkweed, lily of the valley, Siberian ginseng, hawthorn berries
- Repeat serum potassium measurement within 3 to 5 days
- If serum potassium remains ≥ 5.3 and ≤ 5.5 mmol/L, regularly monitor serum potassium levels to ensure stability (suggested once monthly).
- Consider down-titration of study medication, according to investigator's medical judgment.
- Consider down-titration or temporarily discontinue study drug according to investigator medical judgment.
- If serum potassium < 5.5 mmol/L, consider resumption of study drug at lower dose with repeat potassium within 3-5 days

Serum potassium greater than or equal to 6.0 mmol/L

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

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

17. Appendix 5: Guidelines for the management of blood pressure

Guidelines:

1. Investigator should monitor blood pressure closely
2. If symptomatic hypotension occurs:
    a. Correct any treatable cause, e.g. hypovolemia
    b. If hypotension persists, any antihypertensive drug and non-disease-modifying drugs, such as diuretics, CCBs, nitrates, and α-blockers, should be down titrated or stopped first before down-titration of the study drug is considered

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

18. Appendix 6: Guidelines for the management of renal dysfunction

General principles:

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

Two types of response to serum creatinine increase are described:

Surveillance situation

If, at any time after randomization, eGFR decreases by ≥ 25% from baseline (Visit 2) (or if serum creatinine concentration increases to 2.5 mg/dL [221 μmol/L]), the investigator will check for potentially reversible causes of renal dysfunction such as:

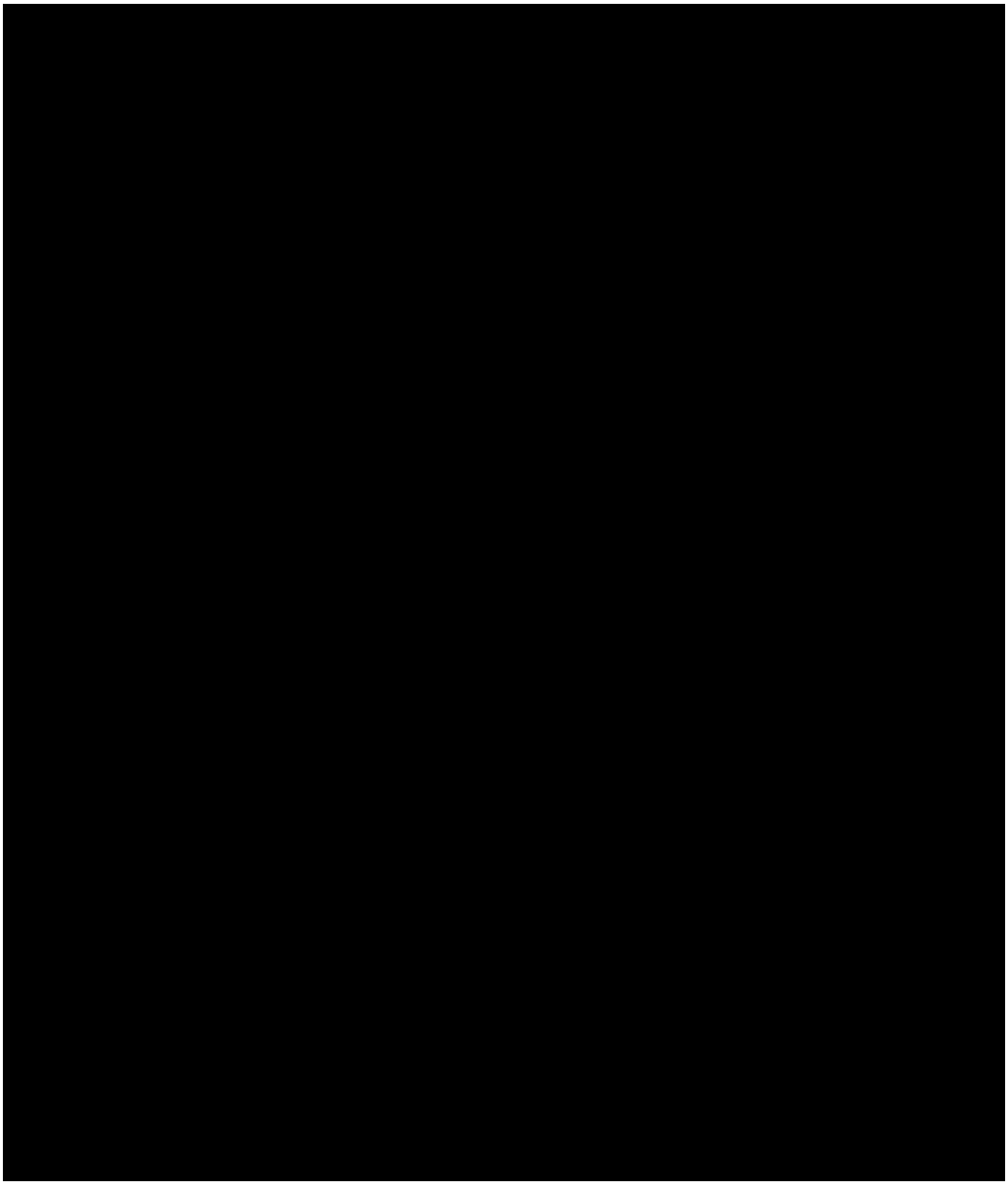
- Non-steroidal anti-inflammatory drug intake, antibiotics, or other treatments known to affect serum creatinine levels
- Volume decrease, including that resulting from excessive dosing of diuretics
- Urinary infection
- Urinary tract obstruction
- Study medication

Action situation

If a patient eGFR decreases by ≥ 40% from baseline (Visit 2) (or if serum creatinine concentration rises above 3 mg/dL (265 μmol/L)), the investigator will check for potentially reversible causes of renal dysfunction (see above).

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

medication was stopped, every effort will be done to restart it again, according to clinical conditions.



20. Appendix 8: IIEF-5

INTERNATIONAL INDEX FOR ERECTILE DYSFUNCTION (IIEF-5)

Over the past 4 weeks:

1. How do you rate your **confidence** that you could get and keep an erection?	1 Very low	2 Low	3 Moderate	4 High	5 Very high

2.	When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	1 Almost never/never	2 A few times (much less than half the time)	3 Sometimes (about half the time)	4 Most times (much more than half the time)	5 Almost always/always
3.	During sexual intercourse, **how often** were you able to maintain your erection after you had penetrated (entered) your partner?	1 Almost never/never	2 A few times (much less than half the time)	3 Sometimes (about half the time)	4 Most times (much more than half the time)	5 Almost always/always
4.	During sexual intercourse, **how difficult** was it to maintain your erection to completion of intercourse?	1 Extremely difficult	2 Very difficult	3 Difficult	4 Slightly difficult	5 Not difficult
5.	When you attempted sexual intercourse, how often was it satisfactory for you?	1 Almost never/never	2 A few times (much less than half the time)	3 Sometimes (about half the time)	4 Most times (much more than half the time)	5 Almost always/always

[a]The IIEF-5 score is the sum of the ordinal responses to the five items; thus, the score can range from 5 to 25.

21. Appendix 9: IIEF-15

INTERNATIONAL INDEX FOR ERECTILE DYSFUNCTION (IIEF-15)

These questions ask about the effect your erection problems have had on your sex life <u>over the past 4 weeks</u>. Please answer these questions as honestly and as clearly as possible. Please answer every question by checking the appropriate box [✓]. If you are unsure about how to answer, please give the most accurate answer you can.

In answering these questions, the following definitions apply:

* **Sexual intercourse**

Is defined as vaginal penetration (entry) of the partner.

** **Sexual Activity**

Includes sexual intercourse, caressing, foreplay and masturbation.

*** **Ejaculate**

Is defined as the ejection of semen from the penis (or the sensation of this).

**** **Sexual stimulation**

Includes situations such as loveplay with a partner, looking at erotic pictures, etc.

1. **Over the past 4 weeks** how often were you able to get an erection during sexual activity**?
Please check one box only.

- No sexual activity ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

2. **Over the past 4 weeks** when you had erections with sexual stimulation****, how often were your erections hard enough for penetration?
Please check one box only.

- No sexual stimulation ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

The next 3 questions will ask about the erections you may have had during sexual intercourse*.

3. **Over the past 4 weeks** when you attempted sexual intercourse* how often were you able to penetrate (enter) your partner?
Please check one box only.

- Did not attempt to initiate sexual intercourse ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

4. **Over the past 4 weeks** during sexual intercourse* how often were you able to maintain your erection after you had penetrated (entered) your partner?
Please check one box only.

- Did not attempt to initiate sexual intercourse ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

5. **Over the past 4 weeks** during sexual intercourse* **how difficult** was it to maintain your erection to completion of intercourse?
Please check one box only.

- Did not attempt to initiate sexual intercourse ☐
- Extremely difficult ☐
- Very difficult ☐
- Difficult ☐
- Slightly difficult ☐
- Not difficult ☐

* **Sexual intercourse:** Is defined as vaginal penetration (entry) of the partner
** **Sexual activity:** Includes sexual intercourse, caressing, foreplay and masturbation
*** **Ejaculate:** Is defined as the ejection of semen from the penis (or the sensation of this)
**** **Sexual stimulation:** Includes situations such as loveplay with a partner, looking at erotic pictures, etc

6. **Over the past 4 weeks** how many times have you attempted sexual intercourse*?
Please check one box only.

- No attempts ☐
- 1-2 attempts ☐
- 3-4 attempts ☐
- 5-6 attempts ☐
- 7-10 attempts ☐
- 11 and more attempts ☐

7. **Over the past 4 weeks** when you attempted sexual intercourse* how often was it satisfactory for **you**?
Please check one box only.

- Did not attempt to initiate sexual intercourse ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

8. **Over the past 4 weeks** how much have you enjoyed sexual intercourse*?
Please check one box only.

- No sexual intercourse ☐
- Very highly enjoyable ☐
- Highly enjoyable ☐
- Fairly enjoyable ☐
- Not very enjoyable ☐
- Not enjoyable ☐

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** **Sexual activity:** Includes sexual intercourse, caressing, foreplay and masturbation
*** **Ejaculate:** Is defined as the ejection of semen from the penis (or the sensation of this)
**** **Sexual stimulation:** Includes situations such as loveplay with a partner, looking at erotic pictures, etc

9. **Over the past 4 weeks** when you had sexual stimulation**** **or** had sexual intercourse* how often did you ejaculate***?
Please check one box only.

- No sexual stimulation or intercourse ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

10. **Over the past 4 weeks** when you had sexual stimulation**** **or** had sexual intercourse* how often did you have the feeling of orgasm with or without ejaculation***?
Please check one box only.

- No sexual stimulation or intercourse ☐
- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

* **Sexual intercourse:** Is defined as vaginal penetration (entry) of the partner
** **Sexual activity:** Includes sexual intercourse, caressing, foreplay and masturbation
*** **Ejaculate:** Is defined as the ejection of semen from the penis (or the sensation of this)
**** **Sexual stimulation:** Includes situations such as loveplay with a partner, looking at erotic pictures, etc

The next 2 questions ask about sexual desire. Let's define sexual desire as a feeling that may include wanting to have a sexual experience (e.g. masturbation or intercourse*), thinking about sex, or feeling frustrated due to lack of sex.

11. **Over the past 4 weeks** how often have you felt **sexual desire**?
Please check one box only.

- Almost always or always ☐
- Most times (much more than half the time) ☐
- Sometimes (about half the time) ☐
- A few times (much less than half the time) ☐
- Almost never or never ☐

12. **Over the past 4 weeks** how would you assess your level of **sexual desire**?
Please check one box only.

- Very high ☐
- High ☐
- Moderate ☐
- Low ☐
- Very low or none at all ☐

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** **Sexual activity:** Includes sexual intercourse, caressing, foreplay and masturbation
*** **Ejaculate:** Is defined as the ejection of semen from the penis (or the sensation of this)
**** **Sexual stimulation:** Includes situations such as loveplay with a partner, looking at erotic pictures, etc

13. **Over the past 4 weeks** how satisfied on average have you been with your **sex life**?
Please check one box only.

- Very satisfied ☐
- Moderately satisfied ☐
- About equally satisfied and dissatisfied ☐
- Moderately dissatisfied ☐
- Very dissatisfied ☐

14. **Over the past 4 weeks** how satisfied have you been with your **sexual relationship** with a partner?
Please check one box only.

- Very satisfied ☐
- Moderately satisfied ☐
- About equally satisfied and dissatisfied ☐
- Moderately dissatisfied ☐
- Very dissatisfied ☐

15. **Over the past 4 weeks** how would you rate your **confidence** that you could get and keep an erection?
Please check one box only.

- Very high ☐
- High ☐
- Moderate ☐
- Low ☐
- Very low ☐

*	**Sexual intercourse:** Is defined as vaginal penetration (entry) of the partner
**	**Sexual activity:** Includes sexual intercourse, caressing, foreplay and masturbation
***	**Ejaculate:** Is defined as the ejection of semen from the penis (or the sensation of this)
****	**Sexual stimulation:** Includes situations such as loveplay with a partner, looking at erotic pictures, etc

22. Appendix 10: Sexual activity diary

1. Within the past 7 days, how often did you try to have sexual intercourse (attempted vaginal penetration) with your partner?

□	not at all (no attempted sexual intercourse within the past 7 days)
□	once
□	twice
□	three times
□	> three times

2. Within the past 7 days, how often have you tried to masturbate?

□	not at all (no attempt to masturbate within the past 7 days)
□	once
□	twice
□	three times
□	> three times

3. Within the past 7 days, how often did you have an erection at night or in the morning (if both apply, please only count once)?

□	not at all (no erection at night or in the morning)

□	once
□	2-3 times
□	4-5 times
□	> 5 times

4. Within the past 7 days, how often have you had intimate physical activity with your partner **other than** having vaginal intercourse (exchange of affection, foreplay, petting, oral intercourse)?

□	not at all (no other sexual activity)
□	once
□	2-3 times
□	4-5 times
□	> 5 times

5. Within the past 7 days, did you avoid physical intimacy with your partner because of your diminished erectile capability?

□	yes
□	no

6. Within the past 7 days, how would you rate your affection/emotions towards your partner?

□	non existent
□	little
□	satisfactory
□	strong
□	very strong

7. Within the past 7 days, to which extent did your sexual desire influence your mood?

□	very negatively affected
□	negative affected
□	not affected
□	positive affected
□	very positive affected