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Department Clinical Development & Medical Affairs Region Europe

Redacted Non-Interventional Study Protocol

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Title	**A**ssessment of **R**eal L**I**fe c**A**re – **D**escribing Europea**N** Heart Failur**E** Management (ARIADNE)
Protocol version identifier	v00 (original protocol)
Date of last version of protocol	25 April 2016
EU PAS register number	ENCEPP/SDPP/13835
Active substance	Sacubitril/valsartan (LCZ696), Angiotensin receptor-neprilysin inhibitors (ARNIs), ATC code C09DX04

Medicinal product and product code

EU marketing authorisation number:	Name	Strength	Packaging size
EU/1/15/1058/001	Entresto	24 mg/26 mg	28 tablets
EU/1/15/1058/002	Entresto	49 mg/51 mg	28 tablets
EU/1/15/1058/003	Entresto	49 mg/51 mg	56 tablets
EU/1/15/1058/004	Entresto	49 mg/51 mg	168 (3 x 56) tablets
EU/1/15/1058/005	Entresto	97 mg/103 mg	28 tablets
EU/1/15/1058/006	Entresto	97 mg/103 mg	56 tablets
EU/1/15/1058/007	Entresto	97 mg/103 mg	168 (3 x 56) tablets

Procedure number	EMEA/H/C/004062

Name of marketing authorization holder(s)	Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7SR, United Kingdom
Joint PASS	No
Research question and objectives	The main objectives of the present NIS are to provide an European picture of (**i**) the demographic and clinical features of symptomatic chronic heart failure patients with reduced left-ventricular ejection fraction (HFrEF) managed in the outpatient sector and the diagnostic and pharmacological interventions they receive and (**ii**) the demographic and clinical features of patients for whom the treating physician decided to start sacubitril/valsartan, the pattern of administration of this drug, the diagnostic and therapeutic interventions these patients receive and the safety and tolerability profile of this drug in real life.
Country (-ies) of study	List of countries is provided in stand-alone document
Author	[redacted]

Marketing authorization holder(s)

Marketing authorization holder(s)	Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7SR, United Kingdom
MAH contact person	[redacted]

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List of abbreviations

ACE	Angiotensin Converting Enzyme
ACEI	Angiotensin Converting Enzyme Inhibitor
ADR	Adverse Drug Reaction
AE	Adverse Event
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor/Neprilysin Inhibitor
BID	Bis In Diem (twice daily)
BNP	Brain Natriuretic Peptide
CHF	Chronic Heart Failure
CI	Confidence Interval
(e)CRF	(electronic) Case Report/Record Form
CRO	Contract Research Organization
CRT	Cardiac Resynchronization Device
CV	Cardiovascular
DMP	Data Management Plan
DS&E	Drug Safety and Epidemiology
EC	Ethic Committee
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ER	Emergency Room
ESC	European Society of Cardiology
EQ-5D	Euroqol 5 Dimension (questionnaire)
GPP	Good Pharmacoepidemiology Practices
HF	Heart Failure
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
ICD	Implantable Cardioverter Defibrillator
ICD-10	The International Classification of Diseases, 10th Revision
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVAD	Left-Ventricular Assist Device
LVEF	Left-ventricular Ejection Fraction
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
NP	Natriuretic Peptide

NT-proBNP	N-Terminal prohormone of Brain Natriuretic Peptide
NYHA	New York Heart Association
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PCI	Percutaneous Cardiac Intervention
QoL	Quality of Life
RAAS	Renin-Angiotensin-Aldosterone System
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SoC	Standard of Care
SOP	Standard Operating Procedure
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UK	United Kingdom
WHO	World Health Organization

1 Responsible parties

Table 1-1 Main responsible parties

Role	Person
Main protocol author	[redacted]
Principal investigator (PI)	[redacted]
MAH contact person	[redacted]

2 Abstract

Title

Assessment of real life care – describing European heart failure management (ARIADNE)

Version and date

Version 00 (original protocol), dated 25-APR-2016

Name and affiliation of main author

[redacted]

Rationale and background

Although Heart Failure (HF) was responsible for approximately 1.6 million hospitalizations per year in the EU recently as judging by ICD-10 I50 coding reported by Eurostat (Eurostat 2014), comprehensive epidemiological data spanning the continent have begun to emerge only relatively recently. In Germany alone, HF was responsible for 386,548 hospitalizations and 46,410 deaths in 2012 as judging by ICD-10 I50 coding reported by the Federal Statistical Office (Statistisches Bundesamt 2013).

While the European Society of Cardiology (ESC) Long-Term Registry aims to describe the clinical epidemiology of outpatients and in-patients with HF across Europe and Mediterranean countries (Maggioni, Anker et al. 2013), a number of European countries did not enroll patients for this registry. In addition, patients treated in the outpatient sector are underrepresented in this registry. Some focused registries like EVITA-HF (von Scheidt, Zugck et al. 2014) have been conducted, but they have often focused on tertiary care centers and may therefore not be representative for the management of European HF patients who are managed by primary care physicians and office-based cardiologists. In general, registries in Europe often show an intrinsic bias toward patients cared for at scientifically interested sites (with an overrepresentation of hospital based care).

REPORT-HF, a global HF Registry sponsored by Novartis, aims to include approximately 20,000 patients worldwide, approximately 14,000 of them in Europe. However, in REPORT-HF patients are enrolled exclusively during a hospitalization for HF and data collection is focusing on the acute phase with merely telephonic follow up of patients. Thus, a prospective non-interventional study capturing chronic HF (CHF) patient management in an office-based European setting is needed in order to obtain a representative picture of CHF management in Europe. Akin to expected variations in CHF management due to national healthcare policies, regional differences e.g. depending on setting (e.g. urban vs. rural), the proximity of specialized HF or cardiology centers, and local budgetary situations, have never been systematically explored in the context of HF management.

With HF mortality remaining at unacceptably high rates, novel treatment approaches are urgently needed. Sacubitril/valsartan (also called LCZ696) constitutes the first of a new class of drugs – Angiotensin Receptor-Neprilysin Inhibitors, ARNIs – designed to replace the current role of ACE inhibitors or Angiotensin receptor blockers (ARBs) in the management of HF. In a recent phase III trial (PARADIGM-HF), sacubitril/valsartan at a target dose of 200 mg BID reduced cardiovascular mortality by 20% compared to a evidence-based dose of the ACE inhibitor enalapril (10 mg BID) (McMurray, Packer et al. 2014). While PARADIGM-HF established a superior efficacy of sacubitril/valsartan with a safety profile comparable to that of enalapril, it appears extremely important to gather additional data on its use and effectiveness in a real life setting, such as which patients are started on sacubitril/valsartan; the pattern of administration of the drug at start and the proportion of patients able to tolerate the drug at different doses; the impact on healthcare resource utilization; quality of life (QoL); main efficacy and safety events in a real-life setting with a more diverse set of patients,

The above mentioned questions will be addressed within the present prospective non-interventional study (NIS). ARIADNE will enroll and describe 12.000 symptomatic CHF patients with reduced left ventricular ejection fraction (HFrEF) treated by specialists in an office-based setting across European countries: 6000 patients treated with current standard of care (SoC) and 6000 patients on sacubitril/valsartan. Enrollment in both cohorts will start in each single country when sacubitril/valsartan is available for use in clinical practice.

Research question and objectives

The main objectives of the present NIS are to provide an European picture of **(i)** the demographic and clinical features of HFrEF patients managed in the outpatient sector and the diagnostic and pharmacological interventions they receive and **(ii)** the demographic and clinical features of patients for whom the treating physician decided to start sacubitril/valsartan, the pattern of administration of this drug, the diagnostic and therapeutic interventions these patients receive and the safety and tolerability profile of this drug in real life.

The **endpoints yielding to the primary objectives** are descriptive in nature and will be derived from the baseline demographic and medical history variables and sacubitril/valsartan treatment data.

Study design

This is an observational, European NIS with prospective collection of primary data. Data will be collected for two groups of HFrEF patients: Symptomatic patients who receive the current individualized standard of care (SoC) for the treatment of CHF and patients for whom the physician has decided to prescribe sacubitril/valsartan. The decision to prescribe sacubitril/valsartan has to be made independently from the participation in this study. This independency is ensured by the fact that patients with any CHF treatment, who satisfy the inclusion and exclusion criteria, can be enrolled. Switching between different CHF treatments (e.g. between SoC and sacubitril/valsartan) is allowed at any time as per decision of the investigator.

Enrollment will start in each country when sacubitril/valsartan is available for clinical use. Assuming that the penetration of sacubitril/valsartan into clinical practice will be slow immediately after launch, the enrollment of sacubitril/valsartan patients will take a significantly longer time than enrollment of SoC patients. At each country level the enrollment of sacubitril/valsartan patients will be continuous, while the enrollment of SoC patients will be divided into two phases, where approximately one half is immediately enrolled at the start of the study and the other half is enrolled during the last part of enrollment into the sacubitril/valsartan group.

All patients, independent of their treatment are to be enrolled consecutively, in order to avoid selection bias.

Population

ARIADNE will include consecutive adult HFrEF patients who are treated by either office-based cardiologists or selected primary care physicians (recognized as HF specialists) all over Europe.

Inclusion criteria

1. Written informed consent provided by the patient or legal representative for participating in the study (according to country specifications)
2. Age ≥ 18 years
3. Patients with symptomatic CHF (NYHA class II – IV) with a documented reduced left ventricular ejection fraction (LVEF) as assessed by clinical examination and any imaging technique performed anytime in the past.

Exclusion criteria

1. Concomitant or planned participation in any interventional clinical trial
2. Patients who are receiving ongoing treatment with sacubitril/valsartan that has been started prior to market launch in their respective country, e.g. within a clinical trial or early access program.

3. Patient still within the safety follow up phase of any previous interventional or non-interventional trial using sacubitril/valsartan (LCZ696), independently whether they received sacubitril/valsartan or the comparator.
4. Acute decompensated HF requiring hospitalization at the moment of enrollment
5. Existing contraindications according to approved product information

Variables

- Demographics (age, gender, living at home or institution, relationship status, education)
- Medical history and comorbidity burden (with focus on duration of HF, etiology of CHF, last hospitalization for HF, cardiovascular conditions, specific comorbidities such as diabetes, renal insufficiency, COPD, anemia, obesity, cancer)
- Clinical Events (CV related and non-CV related deaths and hospitalizations, myocardial infarctions, cerebrovascular incidents)
- Number of visits (other than hospitalization) by provider and primary reason during follow-up
- Diagnostic and therapeutic procedures utilized during follow-up (Results will be collected only as available for blood potassium, blood creatinine, BNP, NT-proBNP and for echocardiographic EF. In all other cases, only documentation if the procedure has been performed and its primary reason)
- Treatment received, both pharmacological and non-pharmacological
- Vital signs and HF signs and symptoms
- Specifically for sacubitril/valsartan: dose at initiation, steps to up-titration, final dose. In case of lack of up-titration, of down-titration or discontinuation, the reason for it will be pursued and recorded in the eCRF.
- EQ-5D and Kansas City Cardiomyopathy Questionnaire (KCCQ) – only in those sites where these questionnaires are part of the routine management of CHF and thus their completion does not affect the non-interventional nature of the present NIS.
- Adverse Events (AEs) and Serious AEs (SAEs), Adverse Drug Reactions (ADRs) and Serious Adverse Drug Reactions (SADRs)

Data sources

This is an observational study with prospective data collection. For some variables, retrospective data shall also be obtained from the patients' medical records (e.g. healthcare utilization in the past 12 months, medical history). The study comprises three visits: at baseline and at approximately 6 months and 12 months after baseline. No exact dates will be enforced for patient visits to avoid interference with usual care. Patients will be enrolled on a consecutive basis. Patient records at the site will be regarded as source data. Sites will be monitored, either with on site or remote monitoring.

Study size

Overall the present NIS will enroll 6000 patients on SoC and 6000 patients on sacubitril/valsartan across Europe.

Data analysis

Only descriptive data analyses will be carried out, supported by calculation of confidence intervals. No statistical testing will be performed.

Analyses will be performed for the total sample and stratified by demographic, anamnestic and medical factors (e.g. sex, duration of HF, severity of HF, previous HF-treatment), using an adequate grouping. As appropriate, analysis of all endpoints will also be carried out after stratification according to CHF treatment during the observation period.

Details on the analysis will be specified in the Statistical Analysis Plan, which will be finalized prior to any data base lock for any analysis (interim or final).

Milestones

[redacted]

3 Amendments and updates

None.

4 Milestones

Table 4-1 Study milestones

Milestone	Planned date
Start of data collection	[redacted]
End of data collection	[redacted]
Interim report	[redacted]
Final report of study results	[redacted]
Registration in the EU PAS register	[redacted]

5 Rationale and background

Although management and therapy of chronic heart failure (CHF) have markedly improved over the last two decades, the prognosis faced by heart failure patients remains poor (Friedrich and Bohm 2007, Mozaffarian, Benjamin et al. 2016).

The prevalence of HF is on the rise because of the increasing life expectancy of the population and the long-time survival of patients with coronary artery disease (Mosterd and Hoes 2007). It is the only cardiovascular disorder that continues to rise both in incidence and in prevalence (Braunwald 2013). Approximately 1-2% of the adult European population has HF, with the prevalence rising to 10% among persons 70 years of age and older (McMurray, Adamopoulos et al. 2012).

Before the modern era of treatment in the 1990s', 60-70% of patients died within 5 years of diagnosis (McMurray, Adamopoulos et al. 2012). Mortality has since then decreased significantly, but has not levelled off anymore since the late 1990s, with a current 3-year mortality remaining above 25% for HF patients above 55 years of age (Barasa, Schaufelberger et al. 2014) and 50% at 5 years (Friedrich and Bohm 2007, McMurray, Adamopoulos et al. 2012). In spite of the introduction of new diagnostic procedures (echocardiography, NT-proBNP), of drug therapies with a proven mortality benefit and of devices such as cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillator (ICD), patients with CHF still face a severe prognosis.

Several explanations for this persistently dismal prognosis are discussed:

- Randomized controlled drug trials in CHF, while showing morbidity and mortality benefits of drug therapies, have excluded important categories of patients such as the elderly with comorbidities, those with significant renal dysfunction or low blood pressure.
- Patients with comorbidities constitute a large proportion of those seen in daily practice by practitioners in the out-patient setting. A Dutch study calculated that 78% of patients older than 80 years seen by primary care physicians are multi-morbid (van den Akker, Buntinx et al. 1998). This is true for HF patients as well. The elderly and comorbid CHF patients are being managed most often by the general practitioners, who are not experts in HF management.
- Heart failure is a heterogeneous disorder, and its diagnosis can be challenging. Heart failure with preserved left ventricular ejection fraction (HFpEF) in particular constitutes a clinical challenge and requires exclusion of other diagnoses before it can be established. Primary care physicians, are less familiar with the necessary distinction between HFpEF and HFrEF making them uncertain about the proper handling of CHF overall.
- Poor drug compliance by HF patients might play a prognostic role as well, through undertreatment, suggesting that new therapeutic options may have neglected quality of life concerns (e.g. drug or device side effects) (Lainscak, Cleland et al. 2007).

Surveys, registries and HF programs have been conducted in order to evaluate compliance by physicians to recommended diagnostic procedures and HF therapy recommended by guidelines. Most registries and surveys show that diagnostic workup for CHF as well as recommended drug therapy are insufficiently applied. Most of the large European Heart

Failure registries have been conducted under the auspices of the European Society of Cardiology (ESC). The recent ESC HF Long Term Registry (Maggioni, Dahlstrom et al. 2013) showed that only 30% of patients receive the target dosage of the drugs recommended by guidelines, but only in two out of three patients, reasons for not reaching target doses were provided (doctor's uncertainty, patient refusal, logistical or cost issues). A more refined understanding of the management of CHF in Europe is hampered by the fact that most large registries, those of the ESC in particular, have recruited from tertiary centers and that in general they mix acute and chronic HF patients. Insufficient data are available about management of CHF in the outpatient sector where a large number of HF patients are managed. HF is a difficult diagnosis for primary care physicians to establish accurately (Hobbs, Doust et al. 2010). The recommended work up with echocardiography and/or BNP or NT-proBNP seems to be performed in only a fraction of the patients in routine primary care physicians' practice, for example in the UK (Hobbs, Doust et al. 2010) or in Sweden (Dahlstrom, Hakansson et al. 2009). Similar to the situation in tertiary centers, adherence to therapeutic recommendations is insufficient in the primary care setting (Calvert, Shankar et al. 2009, Dahlstrom, Hakansson et al. 2009). Adherence to HF recommendations by office-based cardiologists has hardly been studied, though some data suggest improvement is achievable (Fonarow, Albert et al. 2010).

Observing how difficult it is for physicians to reach the recommended target doses of the prognosis-modifying HF drugs has led experts to even question the relevance of current treatment recommendations. A concept of target effect, as opposed to target dose-guided therapy is being suggested (Tavazzi, Maggioni et al. 2013). For the primary care sector taking care of elderly comorbid CHF patients, a Scandinavian team suggests to consider 50% of the recommended target dose of CHF drugs as optimal (Dahlstrom, Hakansson et al. 2009).

Although some insights about the situation in the outpatient sector are available, for the UK or Scandinavia mostly, there is a need for additional real-life data about HF management in the outpatient healthcare sector across a larger variety of European countries.

Recently a new compound, sacubitril/valsartan (LCZ696), the first in class Angiotensin Receptor-Neprilysin Inhibitor (ARNI), has shown remarkable mortality benefit in patients with CHF (McMurray, Packer et al. 2014). Angiotensin receptor blockade (valsartan) is specific and competitive at the angiotensin type 1 (AT1) receptor, which mediates the deleterious effects of angiotensin II on the CV system. The effects of neprilysin inhibition are attributed to the enhanced effects of biologically active natriuretic peptides (NPs). Natriuretic peptides promote natriuresis and vasodilatation by counteracting the renin angiotensin aldosterone system (RAAS) and the sympathetic nervous system and exert direct antifibrotic and antihypertrophic effects on cardiomyocytes (Levin, Gardner et al. 1998, Gardner, Chen et al. 2007, Pandey 2008).

The PARADIGM-HF study was a randomized, double-blind, Phase III outcome trial that evaluated the efficacy and safety of sacubitril/valsartan (at a target dose of 200 mg BID) versus the ACEI enalapril (10 mg BID) in 8,436 HFrEF patients (McMurray, Packer et al. 2014). The primary endpoint was time to first occurrence of either cardiovascular (CV) death or heart failure hospitalization. Sacubitril/valsartan was proven to be superior to the evidence-based dose of enalapril in reducing cardiovascular mortality by 20% and hospitalizations for HF by 21%.

Based on the above described discrepancies between controlled clinical trials and the real-life clinical routine, the present non-interventional study will specifically focus on the outpatient sector, aiming at providing a clear picture of the demographic and clinical characteristics of CHF patients, how they are treated and managed overall, and how sacubitril/valsartan will fit into the day-to-day CHF management in Europe.

6 Research question and objectives

The present non-interventional study will aim to provide a Europe-wide picture of **(i)** the demographic and clinical features of HFrEF patients managed in the outpatient sector and the diagnostic and pharmacologic intervention they receive; **(ii)** the demographic and clinical features of patients the treating physician decided to start sacubitril/valsartan, the pattern of administration of this drug, the diagnostic and therapeutic intervention these patients receive and the safety and tolerability profile of this drug in real life.

Main objectives:

- To describe the profile of patients initiated on sacubitril/valsartan and patients continued on SoC in the outpatient sector in terms of demographics, medical history, HF status, comorbidity burden
- To describe the profile of sacubitril/valsartan patients not reaching and maintaining the target dose of 200 mg twice daily in terms of demographics, medical history, HF status, comorbidity burden as compared with patients reaching the target dose

Additional objectives:

- To describe the overall HFrEF population managed in the outpatient sector in Europe in terms of demographics, medical history, comorbidity burden and previous cardiovascular (CV) events rate
- To describe HF-treatment (pharmacological and non-pharmacological) in the outpatient sector in Europe and in individual countries/country clusters
- To describe the starting dose, titration and maintenance dose of sacubitril/valsartan in patients with different anamnestic and demographic characteristics
- To assess the rates of major HF related outcomes (death, hospitalizations, major CV events)
- To describe Healthcare Resource Utilization in HFrEF patients managed in the European routine practice
- To describe safety and tolerability features of sacubitril/valsartan in real-world HF patients
- To describe the quality of life (QoL) during follow-up (only in those sites where the EQ-5D and/or KCCQ QoL questionnaires are part of routine CHF management)
- To describe the levels of BNP / NT-proBNP (only if these measurements are available or at sites where these measurements are performed within the routine CHF management)

7 Research methods

7.1 Study design

This is an observational, European NIS with prospective collection of primary data. Data will be collected for two groups of HFrEF patients: Patients who receive individualized SoC and patients for whom the physician has decided to prescribe sacubitril/valsartan. If the patient is to be started on sacubitril/valsartan, the decision to prescribe sacubitril/valsartan has to be made independently from the participation in this study. This independency is ensured by the fact that patients with any CHF treatment, who satisfy the inclusion and exclusion criteria, can be enrolled. The treating physician can adapt the CHF treatment during the follow-up phase of the study according to his/her decision. The patients will be followed up over 12 months after enrollment, independently whether they remain on the same CHF treatment they received at the time of enrollment, or are switched to another CHF treatment (see Section 7.2). If during the follow-up phase patients are switched from SoC to sacubitril/valsartan or *vice versa*, they will remain nominally allocated to their original group (i.e. based on their treatment at the time point of enrollment). Details on the analysis of different CHF treatment populations will be provided in the statistical analysis plan.

The main objective of the study is to describe the profiles of symptomatic CHF patients who are prescribed sacubitril/valsartan or SoC in terms of demographics, medical history, HF status, comorbidity burden at the time point of the baseline visit.

A co-primary objective is to describe the profiles of symptomatic CHF patients who are prescribed sacubitril/valsartan and do not achieve and maintain the target dose of 200 mg BID within the observation period of 12 months in terms of demographics, medical history, HF status, comorbidity burden.

The **endpoints yielding to the primary objectives** are descriptive in nature and will be derived from the baseline demographic and medical history variables and sacubitril/valsartan treatment data (see Section 7.3).

Additional endpoints:

- Number of patients achieving a target sacubitril/valsartan dose of 200 mg BID
- Number of patients maintaining the target dose of sacubitril/valsartan 200 mg BID
- Description of SoC treatments (drug and non-drug) according to each participating country (e.g. drug, daily dose).
- Incidence of major CV events and adverse events (AE)
- Change in NYHA status
- Incidence of hospitalizations, doctor visits and diagnostic procedures, and reasons therefore
- Description of baseline health-related quality of life and change of QoL scores throughout the observation period (only in those sites where EQ-5D and/or KCCQ QoL questionnaires are part of routine CHF management)
- Description of baseline BNP / NT-proBNP levels and their changes throughout the observation period (only if measurements are available or in those sites where these measurement are part of the routine CHF management)

7.2 Setting

7.2.1 Population

The present study will include consecutive HFrEF patients treated by office-based cardiologists or selected primary care physicians (recognized as HF specialists) across Europe.

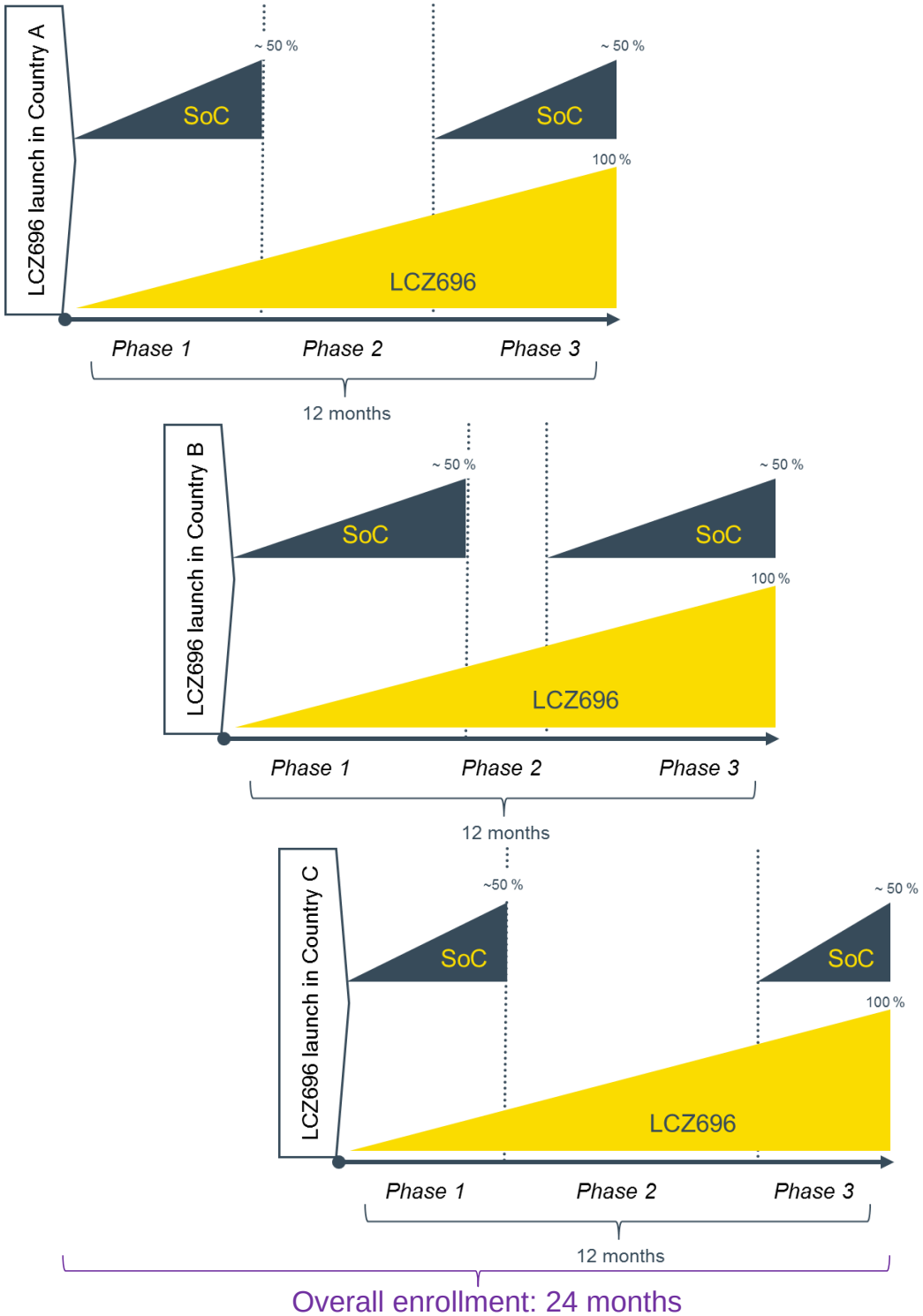
The study [redacted] will include overall 6000 patients on SoC and 6000 patients on sacubitril/valsartan.

Considering that the different local regulations on patient management and reimbursement can significantly impact clinical practice, patient numbers will be allocated to bigger countries and/or clusters of smaller countries with similar healthcare systems in order to ensure the representativeness of the sample.

Enrollment will start in each country when sacubitril/valsartan is available for clinical use. Assuming that the penetration of sacubitril/valsartan into clinical practice will be slow immediately after launch, the enrollment of sacubitril/valsartan patients will take a significantly longer time than including SoC patients. At each country level the enrollment of sacubitril/valsartan patients will be continuous, while the enrollment of SoC patients will be divided into two phases, where approximately one half is immediately enrolled at the start of the study and the other half is enrolled during the last part of enrollment into the sacubitril/valsartan group (see Figure 7-1). By structuring the enrollment of SoC patients in this two-wave pattern, the possibility is created to compare the baseline demographic and medical characteristics of patients that drive the choice of physicians toward individualized SoC or sacubitril/valsartan (main objective) and see if their approach changes over time, after the launch of sacubitril/valsartan.

[redacted]

Figure 7-1 Enrollment schedules (examples) on single country level



Enrollment schedule for each country will depend on enrollment numbers in SoC and sacubitril/valsartan groups and thus might need to be divided into phases, where SoC enrollment is split up in two phases, while LCZ696 enrollment is continuous (examples A-C).
SoC = standard of care, LCZ696 = sacubitril/valsartan

Note: The decision to treat a patient with individualized currently available therapies (SoC) or to start sacubitril/valsartan is to be taken by each investigator according to his/her clinical judgment and independently form participation in this study. Only after that decision is taken, the patient will be enrolled, in order to respect and describe real world clinical practice.

Every effort will be made to reduce selection bias by enrolling patients on a consecutive basis. This also means that patients, who already have been initiated on sacubitril/valsartan treatment after the drug has become commercially available can be included into the study, if they satisfy all inclusion and exclusion criteria and the investigator has the sufficient baseline information (see Section 7.3) on file for these patients.

Follow-up for all patients will last up to 12 months after the baseline visit. The follow-up will consist of 2 visits closest to 6 months and 12 months after the baseline visit, respectively (recommended visit window of ± 2 months). No exact date for the second and final visits will be enforced, to avoid interference with the real life routine care. In case intermediate visit (6 month) will not take place, this will be recorded and described as part of real world practice.

At any time during the study, the investigator is free to adapt or change the patient's CHF treatment as per his/her clinical judgement at any time – the reasons for switching treatments as well as specific details of the new CHF treatment will be documented. The duration of the patient's follow-up is not altered by the switching of therapy, i.e. the individual follow-up duration is only dependent on the time point of the enrollment.

7.2.2 Inclusion criteria

1. Written informed consent provided by the patient or legal representative for participating in the study (according to country specifications).
2. Age ≥ 18 years.
3. Patients with symptomatic CHF (NYHA class II – IV) with a documented reduced left ventricular ejection fraction (LVEF) as assessed by clinical examination and any imaging technique performed anytime in the past.

7.2.3 Exclusion criteria

1. Concomitant or planned participation in any interventional clinical trial
2. Patients who are receiving ongoing treatment with sacubitril/valsartan that has been started prior to market launch in their respective country, e.g. within a clinical trial or early access program.
3. Patient still within the safety follow up phase of any previous interventional or non-interventional trial using sacubitril/valsartan (LCZ696), independently whether they received sacubitril/valsartan or the comparator.
4. Acute decompensated HF requiring hospitalization at the moment of enrollment.
5. Existing contraindications according to approved product information

No additional restrictions for inclusion or exclusion are provided in order to ensure that the patients enrolled are as close as possible to (i.e. representative of) the real population of CHF patients with reduced LVEF managed in the office-based setting.

7.3 Variables

- Demographics (age, gender, living at home or institution, relationship status, education)
- Medical history and comorbidity burden (with focus on duration of HF, etiology of CHF, last hospitalization for HF, cardiovascular conditions, specific comorbidities such as diabetes, renal insufficiency, COPD, anemia, obesity, cancer)
- Clinical Events (both retrospectively over the past 12 months and prospectively, as applicable):
  - Death (CV related and non-CV related, only prospectively)
  - Hospitalizations (defined as at least one overnight staying): number, elective or not, reason for hospitalization (CV related, HF related, non CV related)
  - Myocardial Infarction
  - Stroke
- Number of visits (other than hospitalization) by provider and primary reason during follow-up:
  - Emergency room/department
  - Outpatients office visits (general practitioner; cardiologist; internist; other specialist)
  - Cardiology (day) clinic
  - Device clinic
  - Nurse services/ day clinic
  - Rehabilitation facilities
- Diagnostic and therapeutic procedures utilized during follow-up (Results will be collected only as available for blood potassium, blood creatinine, BNP, NT-proBNP and for echocardiographic EF. In all other cases, the eCRF will only capture if the procedure has been performed and its primary reason)
  - Echocardiogram (LVEF in % if available)
  - ECG / stress ECG
  - Chest X ray
  - Pulmonary function tests
  - Computed Tomography of the Heart
  - Cardiac Magnetic Resonance Imaging
  - Cardiac catheterization
  - Coronary angiography
  - Percutaneous Coronary Intervention (PCI)
  - Coronary artery bypass graft surgery
  - Valve surgery
  - Aortic Valve Replacement (trans catheter or open heart)
  - Percutaneous mitral valve interventions
  - Devices implantation (pacemaker, ICD, CRT, CRT-ICD, LVAD)

  - Heart transplantation
  - 6-minute walk test
  - Selected Laboratory tests (with no other specification)
  - Blood potassium, blood creatinine, BNP and/or NT-proBNP levels (as per local lab)
- Referral pathway that brought the patient to the investigator (for patients who have been treated by the investigator for less than 6 months)
- Ongoing HF treatment and HF treatment received within the last 6 months prior to baseline, both pharmacological and non-pharmacological (physiotherapy, CRT, ICD, rehabilitation). As for ACE-I, ARBs, β-blockers, MRAs, diuretics and ivabradine: substance, dose and frequency of administration will be recorded. As for all other drugs, only the class will be recorded.
- Specifically for sacubitril/valsartan usage: dose at initiation, steps to up-titration, final dose. In case of lack of up-titration, of down-titration or discontinuation, the reason for it will be pursued and recorded in the eCRF.
- The proportion and baseline features of patients not reaching and maintaining the target dose of sacubitril/valsartan will be described: consistently with the definition adopted in the TITRATION study, the target dose is defined as "achieving and maintaining sacubitril/valsartan 200 mg bid without any down-titration or dose interruption over 12 weeks".
- Vital signs (blood pressure, pulse, NYHA status, HF signs and symptoms)
- EQ-5D and/or Kansas City Cardiomyopathy Questionnaire (KCCQ) – only in those sites where these questionnaires are part of the routine management of CHF and thus their completion does not affect the non-interventional nature of the present NIS.
  - The EQ-5D (Dolan 1997) is a widely used generic questionnaire designed to assess health status in adults. The measure is divided into two distinct sections. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). The second section of the questionnaire measures self-rated (global) health status utilizing a vertically oriented visual analogue scale where 100 represents the "best possible health state" and 0 represents the "worst possible health state". This questionnaire will be completed by the patient and collected by the investigator, who will immediately check the questionnaire for remarks by the patient that could indicate adverse events; thereafter the EQ-5D will be entered into the eCRF by the site staff.
  - The KCCQ is a HF-specific questionnaire (Allen, Gheorghiade et al. 2011) and requires on average 4-6 minutes to complete. It covers physical function, clinical symptoms, social function, self-efficacy and knowledge, and Quality of Life (QoL), each with different Likert scaling wording, including limitations, frequency, bother, change in condition, understanding, levels of enjoyment and satisfaction. The KCCQ is a valid, reliable and responsive health status measure for patients with heart failure. This questionnaire will be completed by the patient and collected by the investigator, who will immediately check the questionnaire for remarks by the patient that could indicate adverse events; thereafter the EQ-5D will be entered into the eCRF by the site staff.

- Adverse Events (AEs)/ Adverse Drug Reactions(ADRs) and Serious AEs (SAEs)/Serious ADRs (see Section 9).

7.4 Data sources

This is an observational study with prospective data collection. For some variables, retrospective data shall also be obtained from the patients' medical records (e.g. healthcare utilization in the past 12 months, medical history, prior CHF therapy). The study comprises three visits: at baseline and at approximately 6 months and 12 months after baseline. No exact dates will be enforced for patient visits to avoid interference with usual care. Patients will be enrolled on a consecutive basis. Patient records at the site will be regarded as source data. Sites will be monitored as described in the monitoring plan.

Physicians will record data in an electronic case report form (eCRF) provided by Novartis or designated CRO, which will capture, check, and store the data. The treating physician is asked to complete the eCRF at the time of each visit.

Where applicable, i.e. in countries where these are part of the routine management of CHF, the KCCQ and EQ-5D QoL questionnaires will be applied. The KCCQ and the EQ-5D QoL questionnaire will be completed by the patient, thereafter immediately (within 24 hours) checked by the investigator for remarks hinting at an otherwise unreported adverse event, and subsequently entered by the site staff into the eCRF.

The administration of both questionnaires will occur at baseline (after signature of the ICF and enrollment into the NIS), and during the following 2 visits (around 6 and 12 months after).

Safety data will be transferred to Novartis at a frequency as defined in section 8 of this protocol. Clinical data will be transferred to Novartis after closure of the study.

Data collection schedule

This is a non-interventional study. Therefore no visit schedule will be imposed on participants to avoid interference with routine clinical care. However, based on clinical experience, it seems reasonable to assume that patients visit their treating physicians at least twice a year. Data will be recorded at visits closest to 6 and 12 months (recommended visit window $\pm$ 2 months), performed according to the investigator's practice and judgement. Patients will be treated according to the local prescribing information, and routine medical practice in terms of visit frequency and types of assessments performed and only these data will be collected as part of the study. All items recorded derive from routine clinical care, except informed consent, QoL questionnaires (KCCQ and EQ-5D) and measurements of NT-proBNP blood levels. Therefore, NT-proBNP assessments and QoL questionnaires will be obtained only as available and in those sites where they are part of routine CHF management and thus will not compromise the non-interventional nature of the trial. In all other sites, NT-proBNP testing will be recorded only if available due to the investigator's decision and his/her routine practice and QoL questionnaires will not be assessed.

In general, if any assessment is not done, or information is not available from routine clinical care, this will be documented accordingly.

Table 7-1 Data collection

	Baseline	6 months*	12 months*
Informed consent	X		
Demographics	X	X+	X+
Etiology of HF	X		
History of HF and CV events	X		
Comorbidities	X	X	X
Referral pathway (as applicable)	X		
Vital signs, HF signs and symptoms	X	X	X
Diagnostics and therapeutic procedures	X	X	X
NT-proBNP (as available)	X	X	X
CHF treatment	X[1]	X	X
LCZ696 dose and titration[§]	X	X	X
QoL questionnaires[#]	X	X	X
Adverse Events/ADR/SAE/SADR	X	X	X
Healthcare resource utilization		X	X
End of study assessment			X

*The recommended visit window should be within 2 months before or after the planned date

[#] Only in sites, where part of routine medical management of CHF

[§] Only for patients who receive sacubitril/valsartan

[+] only if relevant changes to certain aspects occurred between visits

[1] only CHF treatment required that is either ongoing at baseline or has been changed within the last 6 month prior to baseline

ADR – Adverse Drug Reactions, SAE – Serious Adverse Event, SADR – Serious ADR

LCZ696 = sacubitril/valsartan

Patients may withdraw consent to continue participation in the registry for any reason at any time. If a patient withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information.

For patients who are missing their appointment of the Follow-up visits, without having stated an intention to withdraw consent, the investigator is asked to exercise "due diligence" by contacting the patient or family or other treating physician, as agreed in the informed consent. These efforts should be documented and any information relevant to the missed visit completed in the eCRF.

7.5 Study size

The main objectives of the ARIADNE study are to describe:

1. The profiles of patients who are prescribed sacubitril/valsartan or SoC in terms of demographics, medical history, HF status, comorbidity burden.
2. The profiles of patients who are prescribed sacubitril/valsartan and do not achieve and maintain the target dose of 200 mg BID within the observation period of 12 months in terms of demographics, medical history, HF status, comorbidity burden.

Overall the present NIS will enroll 6000 patients on SoC and 6000 patients on sacubitril/valsartan. Accordingly, 6000 patients will be available in each group for the first main objective.

In the randomized controlled study TITRATION (Senni 2015), 76.2% of patients were able to reach and maintain the target dose of sacubitril/valsartan over 12 weeks, while 23.8% of patients were not. Despite the absence of other data on the titration of sacubitril/valsartan in the literature, in real-life a higher proportion of patients failing up-titration to the target dose can be expected, due to tolerability reasons and lack of patients' or physicians' compliance. Assuming that the actual lack of up-titration could realistically be as high as 50% of all patients, 3000 sacubitril/valsartan patients will be available for the second of the two main objectives.

The two main objectives are focused on description of patient profiles. With respect to the first main objective, a total of 6000 patients in each group will allow to estimate patient profile parameters with the following precision: The two-sided 95% confidence interval (CI) for qualitative parameters (e.g. gender) will be no longer than 2.6% (i.e. estimate ± 1.3%), and 95% CIs for quantitative parameters (e.g. age) will not exceed 5.0% of the underlying standard deviation (SD) (i.e. estimate ± 0.025*SD).

The number of SoC patients enrolled in phase 1 and in phase 3 respectively (first objective) and the number of patients on sacubitril/valsartan not achieving the target dose (second objective) are expected to be approximately 3000 each. With a sample size of 3000 patients, the two-sided 95% CI for qualitative parameters (e.g. gender) will be no longer than 3.6% (i.e. estimate ± 1.8%), and 95% CIs for quantitative parameters will not exceed 7.2% of the underlying standard deviation (SD) (i.e. estimate ± 0.036*SD).

7.6 Data management

The designated CRO will supply the study site with access to an online eCRF that has been fully validated. Novartis or designated CRO will train designated study site staff on the eCRF system. Alternatively, self-administered online trainings may be applied. Study site staff will not be given access to the eCRF until they have been trained. Designated investigator staff will enter the data required by the protocol into the eCRF using a computer at site. The treating physician must approve that the data are complete and accurate and that all AEs were documented by signing the eCRF. Novartis or the designated CRO can raise manual queries in order to resolve discrepancies resulting from clinical/medical data review.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

At the end of data collection, data entry should be completed by the site and responses to open queries through the site staff should be shared, and data should be signed by a treating site physician. After these actions have been completed, the database will be locked for data analysis. Local laws, regulations and data privacy policies apply.

Data management will be performed by the designated CRO. All data management procedures will be performed in accordance with CRO's standard operating procedures (SOP) and will be described in detail in the project-specific data management plan (DMP).

Statistical analysis is performed using Statistical Analysis System (SAS®, Version 9.2 or higher).

7.7 Data analysis

All analyses will be performed by the designated CRO.

Only descriptive data analyses will be carried out, supported by calculation of confidence intervals. No statistical testing will be performed.

The two patient populations will be considered and analyzed separately. The SoC group will allow the representative picture of current CHF management as mentioned above. The Sacubitril/valsartan stratum will provide early insight into the adoption of this new therapy, once it will be available in the different countries. Therefore also strata for patients switching between SoC and Sacubitril valsartan will be analyzed upon adequate subgrouping.

The two studied groups, SoC and sacubitril/valsartan, are expected to differ significantly depending on the progressive adoption of sacubitril/valsartan by the prescribers – this will be assessed by stratified analysis according to the above described enrollment phases. In addition, besides baseline characteristics of the patients leading to the physicians' decision to prescribe sacubitril/valsartan or continue SoC, no inferences can be made from the comparison of the characteristics of both populations. For the same reason, no comparison of data obtained during the follow-up phase between the treatment groups is planned. Similarly, no safety comparisons will be performed between SoC (where in most cases an established therapy is merely continued) and sacubitril/valsartan (where a new therapy is prescribed).

Analyses will be performed for the total sample and stratified by demographic, anamnestic and medical factors (e.g. sex, duration of HF, severity of HF, previous HF-treatment) using an adequate grouping. Similarly, data will be also analyzed stratified according to enrollment phase (phase 1 and phase 3) and treatment group (e.g. SoC, valsartan/sacubitril, switching between both groups).

The Statistical Analysis Plan will be created as a separate document prior to data base lock for any analysis (e.g. interim analyses, final analysis). This document will contain sufficient details to enable the generation of the analysis of the NIS and specifies:

- the statistical database underlying the evaluation, including all adjustments, implementations and the calculation of derived variables,
- the detailed establishment of the analyzed population(s), and
- the statistical procedures.

7.8 Quality control

7.8.1 Data quality management

All data will be collected via a validated, internet-based electronic data capture (EDC) system. Site personnel will be provided with unique user names and secured passwords in order to use the EDC system. All sites will be fully trained in using the EDC system. CRF completion guidelines will be shared with every site.

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.

Designated CRO or a third party on behalf of the sponsor can raise manual queries in order to resolve discrepancies resulting from clinical/medical data review. To assure database quality, edit checks will be programmed in accordance with the data validation plan. The data entered into the eCRF will be checked automatically for completeness and accuracy. In case of missing relevant data or discrepancies, error messages or queries will be generated automatically by the system.

Designated CRO will assure database quality processes are followed including review of the data entered into the CRFs by investigational staff for completeness and accuracy, and in accordance with the data validation plan.

Local laws, regulations and data privacy policies apply.

7.8.2 Data recording and document retention

In all scenarios, the physician 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, and the results of any other tests or assessments. All information entered in the CRF must be traceable to these source documents in the patient's file.

The physician must give Novartis (or designee) access to all relevant source documents to confirm their consistency with the CRF entries. No information in source documents about the identity of the patients will be disclosed.

Novartis and designated CROs will follow their applicable Standard Operating Procedures (SOPs) regarding retention of records. The physician must keep the original informed consent form signed by the patient (a signed copy is given to the patient and the patient's legal proxy, if applicable).

Informed consent forms must not be shared with the sponsor and local data privacy policies apply.

7.8.3 Site monitoring

Formal site monitoring will be performed as described in the Monitoring Plan for this study.

The designated CRO will assure compliance monitoring.

7.9 Limitations of the research methods

Potential limitations of the present study are due to its non-interventional character, where no stipulation regarding data collection can be made. In the present study, not all involved sites use QoL questionnaires or certain lab parameters within the routine management of CHF and thus, these data will not be available for all patients. In addition, there is no randomization or blinding within a NIS; especially QoL data from non-blinded patients need to be interpreted carefully. However, the non-interventional character of the study is the only way to obtain real-life data. In order to obtain a representative sample of the population of CHF patients from the outpatient sector, the ARIADNE NIS will not mandate diagnostic nor therapeutic processes which would distort the recruitment.

However, non-cardiac disorders as well as HFpEF (HF with preserved systolic function) can be confused with HFrEF. In order to ensure sufficient homogeneity of the patient population, inclusion will require that the patient has documentation of reduced left ventricular systolic function (LVEF) in the past through any imaging technique.

To reduce the selection bias in the patients an investigator will include into the NIS, the physician is urged to offer enrollment to all consecutive patients and not select patients from his patient database. However compliance with this requirement cannot be verified due to data privacy regulations; therefore the investigators are asked to diligently follow the good epidemiological practice requirement of offering participation to this study to consecutive patients.

A potential selection bias might arise from the bi-phasic enrollment of SoC patients. This risk is mitigated by following design features:

- there is no minimal time requirement for the patient being on SoC prior to enrollment into the study and
- patients can be switched to the optimal therapy as per judgement of the investigator at any time of the study.

Thus, there is no incentive for increased prescribing (and therefore for a selection bias) sacubitril/valsartan during phase 2 of enrollment (when enrollment into the SoC group is paused). If a patient is receiving SoC during enrollment phase 2 and still would like to participate in the NIS when enrollment into this group is commenced again (i.e. phase 3) he/she can be enrolled into the SoC group at that time, as there are no temporal stipulations regarding duration of SoC treatment.

The lack of such a temporal stipulation of SoC treatment might indeed be considered a further limitation of this study, similarly to lack of such stipulations regarding other potentially confounding factors, such as duration of CHF, prior treatments, disease severity etc. Such limitations are however typical for non-interventional studies, which aim to assess the real-life situation and where the enrolled population per se is not homogeneous and a certain homogeneity can only be achieved not by stringent inclusion criteria, but only by adequate and medically justified stratification and sub-grouping prior to analysis.

7.10 Other aspects

7.10.1 Steering Committee

Between six and eight external experts and one to two Novartis associates will be appointed to the steering committee of this NIS. The scope of the steering committee's mandate is:

- Make recommendations for the NIS protocol and its amendments
- Make recommendations for operational questions of study conduct including, but not limited to, site selection, local study meetings and newsletters
- Review enrollment data and final study data
- Make recommendations for publication of study data

8 Protection of human subjects

The treating physician must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and the patient enrollment log must be kept strictly confidential to enable patient identification at the site.

For audits, inspections or routine monitoring, source data and signed informed consent forms as well as the patient enrollment log must be available to Novartis representative or Health Authorities.

Patient data will be entered by the physician into the eCRF in a pseudonymized manner according to legal, compliance and regulatory requirements (unique patient number). Only the physician will be able to allocate the patient number to the patient's identity. The physician must maintain the patient identification list and source documents for each participating patient. No information in source documents about the identity of the patient will be disclosed.

For analysis and publication purposes, data will be only presented in an anonymized manner, i.e. at population and not individual patient level.

The study may be reviewed while it is in progress. This review may be conducted by the authorities or Novartis to ensure that the rules are followed and quality is maintained. All persons involved in the study must respect the strictest confidentiality. The name of the patients will never be published in any reports or publications, neither in print nor on the internet, nor in any other place.

Regulatory and ethical compliance

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in non-interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of

Observational Studies in Epidemiology) guidelines (von Elm, Altman et al. 2008), and with the ethical principles laid down in the Declaration of Helsinki.

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board / Independent Ethics Committee (IRB/IEC) before study start according to local regulations. Approval letters concerning protocol and informed consent will be filed by Novartis

Informed consent procedures

The physician must keep the original informed consent form signed by the patient (a signed copy is given to the patient).

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/EC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient according to country specifications. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before any data are collected. The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to treating physicians or other involved medical professionals in a separate document a proposed informed consent form that complies with the Declaration of Helsinki principle and regulatory requirements and is considered appropriate for this study.

9 Management and reporting of adverse events/adverse reactions

All adverse events (AEs), including serious adverse events (SAEs), occurring in patients treated with sacubitril/valsartan will be collected and recorded in the eCRF as well as in the Novartis safety database, irrespective of causal association to sacubitril/valsartan. Adverse Drug Reactions (ADRs) occurring in association with exposure to Novartis drug other than sacubitril/valsartan, should be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting and to Novartis DS&E as a spontaneous report. All adverse reactions identified for non-Novartis products should be reported to the local Medicines Committee/Health Authority in accordance with national regulatory requirements for individual case safety reporting or the Marketing Authorization Holder as these will not be recorded in the Novartis safety database.

Investigators will be instructed to report all serious adverse events (SAEs) to Novartis within 24 hours of learning that the SAE occurred. Investigators will be instructed to report all non-serious AEs to Novartis within 10 days of awareness of the non-serious AE. The requirements are summarized in Table 9-1 below.

The telephone and telefax number of the contact persons in the local Novartis department of DS&E (Drug Safety and Epidemiology), specific to the site, are listed in the treating physician or other involved health care professional folder provided to each site.

Table 9-1 Adverse event and adverse drug reactions – summary of reporting requirements

Current treatment at the time of event onset	SoC	Sacubitril/valsartan
Non-serious adverse events without causal relationship to respective treatment (i.e. non-serious adverse event, nsAE)	No AE documentation required	Enter within 10 days into eCRF
Non-serious adverse events with causal relationship to respective treatment (i.e. non-serious adverse drug reaction, nsADR)	• Report to local health authority as per local regulations. • In case Novartis drug, additionally report to Novartis DS&E as spontaneous report.	• Enter within 10 days into eCRF • Reporting to local health authority will be performed by Novartis DS&E based on eCRF entry
Serious adverse event without causal relationship to treatment (i.e. SAE)	No AE documentation required	• Report to Novartis DS&E within 24h of awareness • Enter within 24h into eCRF
Serious adverse event with causal relationship to respective treatment (i.e. SADR)	• Report to local health authority as per local regulations. • In case Novartis drug, additionally report to Novartis DS&E as spontaneous report	• Report to Novartis DS&E within 24h of awareness; to local health authority will be performed by Novartis DS&E • Enter within 24h into eCRF

An adverse event is any untoward medical occurrence in a patient participating in this study (after signing the ICF) that does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug of interest, whether or not related to the medicinal product(s).

Drug of interest is the drug under evaluation (sacubitril/valsartan) given at any time during the study. Medical conditions/diseases present before the Baseline visit are only considered adverse events if they worsen after start of study (Baseline visit).

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

Abnormal laboratory data or test results should only be documented as adverse events if:

- There is a change in terms of a worsening of respective parameters compared to the baseline (baseline visit). This requirement is not applicable if there is no previous baseline value.

  AND

- Altered lab parameters

- Are classified as clinical relevant OR
- Come along with clinical signs and symptoms OR
- Indicate a therapeutic intervention OR
- Lead to a dose reduction and / or temporary interruption or permanent discontinuation of the investigational drug in the NIS

In such cases they must be documented as AEs. Changes of a quantifiable parameter must be documented as SAE in the following cases, if:

- Formal criteria of SAE are met (see definition SAE)
- It exceeds or falls below the pre-determined limit for the respective parameter

Adverse event reporting

All adverse events occurring **in patients taking sacubitril/valsartan** (see Table 9-1) must be recorded on the Adverse Events eCRF containing the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the drug(s) of interest (suspected/not suspected)
   For the causality assessment between drug and event, there is the choice between "no causal relationship" or "causality suspected". A medical causality assessment is mandatory and must be documented in any case. It should be considered that many aspects play a role in the causality assessment. These aspects may concern the individual patient, the underlying disease, comorbidities, any existing concomitant medication or not drug-related factors.
   - No causal relationship: There is no reasonable opportunity of a causal relation between the drug and the AE.
   - Suspected causal relationship: There is a reasonable opportunity of a causal relation between the drug and the AE
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE, see below)

In addition, all reports of the following special scenarios are also considered an adverse event irrespective if a clinical event has occurred:

- Drug-drug or drug-food interaction
- Drug use during pregnancy or lactation
- Lack of efficacy
- Overdose
- Intentional drug abuse and misuse
- Medication errors including drug maladministration
- Dispensing or prescribing errors
- Drug dependence or addiction
- Withdrawal reaction/syndrome or rebound symptoms
- Unexpected beneficial effect
- Treatment non-compliance (with clinical symptoms)

Note: Occupational or accidental exposure, for example of study personnel or family members of the patient should be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or Novartis DS&E as a spontaneous report.

Any treatment of any adverse event should be recorded on the Adverse Event CRF. Some examples of treatment to be recorded are: no action taken (i.e., further observation only); drug of interest dosage adjusted/temporarily interrupted; drug of interest permanently discontinued due to this adverse event; treatment medication introduced or adjusted; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged.

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

Information about common adverse effects already known about the medicinal product can be found in the locally available labeling document for the approved indication under evaluation in this study and should be discussed with the patient prior to study start and during the study as needed.

Adverse events of special interest (AESI)

In case of adverse events of particular interest (for sacubitril/valsartan these include angioedema, hepatotoxicity related events, cognitive impairment and statin related events), additional information concerning the event must be documented. After such events have occurred and have been entered into the eCRF, corresponding questionnaires will be provided by the local Novartis DS&E on a case-by-case basis

Serious adverse events (SAE)

In principle, a distinction is made between non-serious and serious adverse events (SAE).

A SAE is defined as an event which:

- is fatal
- is 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, e.g. hospitalization for diagnostic procedures.
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the drug of interest
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition

- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above e.g. may require 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

Note: The assessment of whether an SAE applies only depends on whether one of the aforementioned formal criteria applies. It is independent of any assessment of the question whether there is possibly a causal relationship between administration of a medicinal product and the occurrence of the SAE.

Note: Transmission of infectious disease via medication is considered to be a serious adverse reaction and should be reported and assessed as medically significant in the absence of other seriousness criteria.

Note: A ***progression of the underlying disease*** while receiving treatment with the drug studied in this NIS can be documented as an adverse event (AE) only if a causal connection with the treatment with the drug studied in this NIS is suspected, or if as a result of disease progression one or more of the formal criteria for a serious adverse event (SAE) listed under the SAE definition is/are met.

SAE reporting

To ensure patient safety, every SAE in patients taking sacubitril/valsartan (see Table 9-1), regardless of causality assessment, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of the Novartis drug of interest taken or last visit whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence (see below).

Any SAEs reported more than 30 days after study termination should only be reported to Novartis if the treating physician or other involved health care professional suspects a causal relationship to the Novartis drug of interest.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the treating physician or other involved health care professional receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs in patients taking sacubitril/valsartan is collected and recorded on the Serious Adverse Event eCRF – this information needs to be entered into the eCRF within 24 hours of awareness. Depending on local reporting requirements, there may be two ways of submitting the SAE information to Novartis DS&E:

- **Paper SAE Form:** Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The treating physician or other involved health care professional must assess the relationship to the Novartis drug of interest, complete the SAE Report Form and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety & Epidemiology (DS&E) Department. The telephone and telefax number of the contact persons in the local department of DS&E, specific to the site, are listed in the treating physician or other involved health care professional folder provided

to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

- **Via eCRF:** The SAE information is submitted electronically to DS&E after entering into the eCRF. The treating physician or other involved health care professional must assess the relationship to the Novartis drug of interest, complete the SAE eCRF within, electronically sign it and initiate the report transmission to the local Novartis Drug Safety & Epidemiology (DS&E) Department within 24 hours after becoming aware of the SAE. In case of technical problems, a transmission of the report via fax or telephone is possible (see above).

Follow-up information

Note that follow-up information on SAE is to be provided within 24 hours of awareness of new information on an existing SAE.

Follow-up information on SAE can be provided by two different ways, depending on the local reporting requirements in your country:

- **Paper SAE Form**: A follow-up is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or withdrew from study participation.

- **Via eCRF**: Follow-up information on SAE is provided by updating the respective section in the eCRF and initiation transmission of the SAE report again; note that follow-up information on SAE also needs to be verified by electronic signature of the investigator/treating physician. Note that follow-up information on SAE is to be provided within 24 hours of awareness of new information on an existing SAE.

Note: If the SAE is not previously documented in the Sacubitril/valsartan SmPC, a local DS&E Department associate may urgently require further information from the treating physician or other involved health care professional for Health Authority reporting

Follow-up information on non-serious AE is to be provided by updating information in the eCRF within 10 days of awareness of new information on an existing non-serious AE.

Pregnancies

Any occurrences of a pregnancy in a patient (or a patient's partner) during study participation will also be collected. Reports of pregnancies during which Novartis products have been used or continue to be used represent important safety information to Novartis that helps to ensure and improve the patient safety in relation to Novartis products.

Pregnancies under treatment with non-Novartis products should be reported to the local Medicines Committee/Health Authority in accordance with national regulatory requirements.

Any pregnancy during therapy with a Novartis product, irrespective of whether or not it is associated with an AE/SAE, must be reported to the Drug Safety department of Novartis within 24 hours of it becoming apparent. The pregnancy must be documented on a separate "Pregnancy Form" and reported to the local Novartis DS&E by the investigator.

The progress of the pregnancy should be monitored in order to record the outcome of the pregnancy, including any spontaneous and planned terminations, details of the birth and the presence or absence of any birth defects, congenital anomalies or complications in the mother or newborn child. Such information on the progress of the pregnancy/follow-up information on the birth should be documented on the same 'Pregnancy Case Report Form'.

Every adverse event (AE/SAE) occurring during a pregnancy must be documented additionally in the SAE section of the eCRF within 24 hours of awareness.

10 Plans of disseminating and communicating study results

Upon study completion and finalization of the study report, the results of this non-interventional study may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

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12 Annexes

12.1 Annex 1 – List of stand-alone documents

Table 12-1 List of stand-alone documents

Number	Document reference number	Planned Date	Title
1	Will be generated after protocol finalization in document management system	30 Apr 2016	List of participating countries
2	Will be generated after protocol finalization in document management system	30 Apr 2016	Enrollment description document