NOVARTIS

Global Clinical Development - General Medicine

Clinical Trial Protocol / NCT02807857

a Prospective evaluation of natRiuretic pEptide based reFerral of CHF patiEnts in pRimary care - PREFER

Document type:	Clinical Trial Protocol
EUDRACT number:	2016-000473-20
Version number:	00 (Original Protocol)
Clinical trial phase:	Low-interventional study
Release date:	15-Feb-2016

Clinical Trial Protocol Template Version 03 (August 2015)

[redacted]

Disclaimer:

This low-interventional research project should be submitted to Ethics Committees and regulatory authorities (only if applicable) according to local laws and regulations.

The study identification is coded for technical reasons as CLCZ696B3402 to allow for oversight and tracking in the sponsor's data bases and systems, even though the project is not targeting a specific medicinal product and no study medication is stipulated.

[redacted]

Table of contents

[redacted]

[redacted]

[redacted]

List of tables

List of figures

[redacted]

List of abbreviations

ACE	Angiotensin Converting Enzyme
AE	Adverse Event
AT1R	Angiotensin Receptor 1
BNP	Brain Natriuretic Peptide
CFR	US Code of Federal Regulations
CDS	Core Data Sheet (for marketed drugs)
CHF	Chronic Heart Failure
CI	Confidence Interval
ClinRO	Clinician Reported Outcome
COPD	Chronic Obstructive Pulmonary Disease
CPO	Country Pharma Organization
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTC	Common Terminology Criteria
CTRD	Clinical Trial Results Database
CV	Cardiovascular
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
ER	Emergency Room
ESC	European Society of Cardiology
eGFR	Estimated Glomerular Filtration Rate
GCP	Good Clinical Practice
HF	Heart Failure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left Ventricular Ejection Fraction
MAH	Market Authorization Holder
MedDRA	Medical dictionary for regulatory activities
NP	Natriuretic Peptide
NT-proBNP	N-Terminal prohormone of BNP
PRO	Patient Reported Outcome
QoL	Quality of Life
RAAS	Renin Angiotensin Aldosterone System
SAE	Serious Adverse Event
SR	Spontaneous Report
UK	United Kingdom
WHO	World Health Organization

[redacted]

Glossary of terms

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

[redacted]

Protocol summary

Protocol number	CLCZ696B3402
Title	A prospective evaluation of natriuretic peptide based referral of CHF patients in primary care
Brief title	A prospective evaluation of natriuretic peptide based referral of CHF patients in primary care
Sponsor and Clinical Phase	Novartis
Investigation type	other
Study type	Low-interventional, observational.
Purpose and rationale	In the majority of European countries, the primary management of chronic heart failure (CHF) patients is performed by general practitioners in collaboration with cardiologists (specialists). Previous studies have shown that many patients suffering from CHF do not receive optimal pharmacological and/or device treatment for their disease. An increase in natriuretic peptides is associated with increased risk of cardiovascular events in heart failure patients. The purpose of the present study is to assess if a referral of clinically stable CHF patients with reduced ventricular ejection fraction (EF≤40%) with NT-proBNP levels ≥ 600 pg/ml to a specialist (cardiologist) will lead to treatment optimization, defined as adherence to the treatment recommendations according to the ESC guidelines. In addition, data obtained in this study will be used to describe demographic, clinical (including NT-proBNP levels) and treatment characteristics of CHF patients who are managed in the primary care setting across Europe.
Primary Objective(s)	To assess if NT-proBNP measurement-guided cardiologist-referral of CHF patients, who are currently judged by their primary care physician as being clinically stable*, leads to optimization of HF treatment, defined as adherence[#] to level I-A treatment recommendations of the current[§] ESC guidelines for the treatment of HF. ***Note:** Within this study, clinically stable patients are defined as those patients, who by the judgement of their primary care physician currently do not require and, in the last 3 months prior to the baseline visit have not had, any change in their pharmacological or device treatment of HF. [#]**Note:** Adherence to the recommendations of the ESC guidelines within this study is defined as the prescription of all HF specific drugs with level I-A recommendation for a given patient's clinical status at a dose > 50% of the recommended daily dose. [§]**Note:** Current ESC guidelines are those which are in force on the date the patient signs the informed consent form.
Secondary Objectives	To describe the baseline demographic and clinical characteristics, as well as pharmacological and device treatment of CHF patients managed in the primary care setting (in the total population of enrolled patients and also sub-grouped into different European country and patient characteristics clusters).

[redacted]

	To assess in clinically stable patients the impact of patients' key baseline characteristics on the cardiologists' and primary care physicians' prescription practice for HF treatment and the adherence of these treatment choices to the recommendations of the current ESC guidelines. To describe the blood levels of NT-proBNP in CHF patients managed in the primary care setting. To describe the proportion of CHF patients managed in the primary care setting considered as being clinically stable according to the above definition. To describe local prescription practice of cardiologists for the treatment of clinically stable CHF patients with NT-proBNP levels ≥ 600 pg/ml. To describe local prescription practice and decision making of primary care physicians for the treatment of clinically stable CHF patients with NT-proBNP levels ≥ 600 pg/ml. To characterize how treatment optimization, defined as prescription of treatment regimens adherent to the recommendations of the ESC guidelines, affects NT-proBNP levels in clinically stable CHF patients with baseline NT-proBNP levels ≥ 600 pg/ml. To assess the baseline health-related quality of life (QoL) in CHF patients and describe the temporal course of QoL after specialist referral in clinically stable CHF patients with NT-proBNP ≥ 600 pg/ml, by means of EuroQoL EQ-5D and KCCQ questionnaires.
Study design	This is a low-interventional, prospective, study enrolling patients with chronic heart failure who are managed in the primary care setting across Europe. The study comprises three visits over a period of maximum 10 months. Enrollment is planned to last 24 months. At baseline (**visit 1**) for all consecutive patients, who satisfy the inclusion and exclusion criteria, the demographic and clinical characteristics, their current therapy regimen for the treatment of HF, any concomitant medication and their baseline QoL will be documented (EQ-5D, KCCQ). At this visit, after the investigator documents his/her decision whether the patient is considered being clinically stable, all patients (clinically stable and not stable) will have a blood test for assessing NT-proBNP levels. Only patients who are considered being clinically stable by the investigator and who show NT-proBNP blood levels ≥ 600 pg/ml will enter the prospective period of the study. The Patients will be referred to a cardiologist for evaluation of their HF treatment. After the referral visit to the specialist's office, the patient will return to the primary care physician for **visit 2**. During visit 2 the primary care physician will evaluate and record the recommendations provided or treatment changes introduced by the specialist and will make and record his/her decision on the patient's future HF treatment. In addition, EQ-5D and KCCQ questionnaires will be filled out by the patient at this visit. The patients in the prospective period will have a final visit (**visit 3**), where they will be asked to fill out two QoL questionnaires (EQ-5D, KCCQ) again, will have their vital signs and medication documented and a final NT-proBNP measurement will be obtained.

[redacted]

Population	The study population will consist of adult (≥ 18 years) male and female patients with chronic heart failure with reduced ejection fraction (LVEF ≤ 40%) who are currently managed in a primary care setting in sites across Europe.
Key Inclusion criteria	• Willing and able to provide written informed consent and accept study procedures and time schedule. • Age ≥ 18 years. • Patients suffering from chronic heart failure (the heart failure diagnosis must have been made or confirmed by a cardiologist and/or hospital physician at any time point in the patient's medical history). • Patients with reduced ejection fraction (LVEF ≤ 40%) as confirmed at any time point in the patient's medical history.
Key Exclusion criteria	• Use of investigational drugs within 5 half-lives of enrollment, or within 30 days /until the expected pharmacodynamic effect has returned to baseline, whichever is longer. • Major surgery in the last 3 months or planned/foreseeable major surgery or cardiac intervention during the study. • Cancer or other significant co-morbidities implying that the patient's condition is unstable. • Comorbidities that can be associated with elevated natriuretic peptide (NP) levels: renal insufficiency, (eGFR < 25 ml/min/1.73 m² calculated according to MDRD formula), recent (less than 3 months) cerebral trauma or recent (less than 3 months) cerebrovascular incident, novel diagnosis or acute exacerbation of COPD within the last 3 months. • Patients who are primarily managed and regularly followed-up by a cardiologist for their HF. • Highly frail patients whose estimated lifespan due to comorbidities is less than 6 months.
Study treatment	Not applicable. There is no treatment stipulated by this protocol.
Efficacy assessments	Not applicable. There are no efficacy assessments in this study.
Key safety assessments	Adverse event monitoring, Physical examinations, monitoring of safety lab parameters (if available within the investigator's clinical routine).
Other assessments	Assessment of patient reported outcomes (Quality of Life) is planned in this study using the EQ-5D and KCCQ questionnaires. Patients' demography, medical history and HF-treatment will be assessed. Therapy for HF at baseline and after consultation with a cardiologist, i.e. at visit 2 and visit 3, will be documented and assessed. [redacted] NT-proBNP levels will be measured by means of an on-site device, and will be documented and assessed.
Data analysis	Analyses of baseline variables will be carried out on all patients who signed the study information consent (Enrolled Set). Analyses regarding the prospective period of the study will be carried out on all patients who have entered the prospective period of the study (Follow-up Set).

[redacted]

	The variables used for the primary analysis are the assessment of the patient's treatment at baseline (A1) and the assessment of the patient's treatment at visit 2 (A2) with respect to the adherence to the current ESC guidelines. Cross-tabulation between the variables A1 and A2 will be displayed showing absolute and relative frequencies. The analysis yielding to the primary objective will be performed by estimating the proportion of patients who are switched to an ESC guideline recommendation-adherent regimen after referral to a cardiologist based on all referred patients whose treatment does not adhere to these recommendations. A respective 95%-confidence interval (CI) will be provided for this proportion. The analysis of the primary endpoint will be performed on all enrolled patients entering the prospective period of the study. Analysis of secondary variables in the Follow-up Set will be additionally, stratified by the assessment of the treatment before and after referral to a cardiologist (*ESC non-conform/ESC conform*, *ESC non-conform/ESC non-conform*, *ESC conform/ESC conform*, *ESC conform/ESC non-conform*).
Key words	low-interventional observational study, heart failure, primary care, Europe

[redacted]

1 Introduction

1.1 Background

Chronic heart failure (CHF) is a common chronically progressive syndrome, with an estimated point prevalence of 1-2% that is increasing with age (McMurray, Adamopoulos et al. 2012).The syndrome is characterized by a severe prognosis (Hobbs, Doust et al. 2010) and is one of the most cost demanding medical conditions in the Western world (Hobbs, Doust et al. 2010). Progress made in the past two decades has yielded evidence based strategies significantly reducing CHF mortality and morbidity; the effects of targeted multi-drug therapies (Parikh and Kadowitz 2013), patient centric outpatient management systems (Wakefield, Boren et al. 2013) as well as advances in implantable devices (Kuck, Bordachar et al. 2014) are all well proven.

Natriuretic peptides (NP) are endogenous hormones produced by, amongst other tissues, the heart and released in response to myocardial wall stress and/or overload (Del Ry, Cabiati et al. 2014). The mode of action and the effects of the NP release in CHF are yet to be completely elucidated, however numerous studies indicate that the NP release and increase is positively correlated with the severity of HF. It is also hypothesized that the increased circulating NP during HF may contribute to a compensatory mechanism in the failing heart, counteracting many of the detrimental pathophysiological cascades seen in HF by increasing natriuresis, diuresis, vasorelaxation and possibly reducing mal-adaptive cardiac remodeling (Del Ry, Cabiati et al. 2013) . The use of NP levels as a laboratory parameter, especially BNP and its amino-terminal propeptide equivalent (NT-proBNP), is recommended in the European Society of Cardiology (ESC) guidelines to "exclude alternative causes of dyspnea (if the level of NP is below the exclusion cut-point, HF is very unlikely)" and to "obtain prognostic information" (McMurray, Adamopoulos et al. 2012). Some studies in the literature also suggest that BNP/NT-proBNP could be used to guide HF treatment, ultimately providing a clinical benefit (Troughton, Frampton et al. 2014, Pruett, Lee et al. 2015). Levels of NPs have also been shown, in a limited number of studies, to be related to outcome, where elevated levels of NT-proBNP significantly increase risks of adverse outcomes (Januzzi, Sakhuja et al. 2006, Masson, Latini et al. 2008, Flint, Allen et al. 2014).

The daily follow up of CHF patients in Europe lies mostly within the responsibility of primary care physicians. A significant amount of primary care physicians have difficulties with the precision of diagnosing HF (Fonseca 2006) due to the unspecific nature of signs and symptoms of HF and, due to different reasons, HF patients' therapy and monitoring in primary care could be optimized (Cleland, Cohen-Solal et al. 2002, Calvert, Shankar et al. 2009). In 2009, Dahlstrom and colleagues performed an observational multicenter study on the treatment of CHF with more than 2000 patients by primary care physicians in more than 200 centers in Sweden. They showed that only 42% of patients were on treatment with Renin Angiotensin Aldosterone System (RAAS) inhibitors and beta blockers and that only 20% of patients were receiving doses ≥ 50% of the doses recommended by the ESC guidelines (Dahlstrom, Hakansson et al. 2009).

[redacted]

The beneficial effect of an increased collaboration between primary care physicians and specialists has been previously reported (Singh, McGregor et al. 2014). A recent study involving chart reviews of HF patients showed that the proportion of patients prescribed optimal, evidence based doses of ACE-inhibitor/AT_1R-blocker and beta blocker was 69 %, 33 % and 25 % for patients treated by interdisciplinary physician teams, cardiologists and primary care physicians, respectively ($p < 0.0167$) (Crissinger, Marchionda et al. 2015). Additionally, published evidence shows that treatment of CHF in a specialty care setting is often more adherent to ESC guideline recommendations. Maggioni et al reviewed the treatment of 12.440 patients from the ESC Heart Failure Long-Term Registry from 211 cardiology centers across Europe, and showed that RAAS inhibitors, beta blockers and mineralocorticoid antagonists were prescribed in the vast majority of patients (respectively 92, 93 and 67% of cases) (Maggioni, Anker et al. 2013). In respectively 29, 24 and 17% of cases the dose was on target; in about an additional 30% drugs were being up-titrated and in about another 30% a clinical reason for under-dosing was clearly defined (Maggioni, Anker et al. 2013).

A study performed in 2009 by a group of investigators in the UK included a systematic review of the literature and a meta-analysis of individual patient data set in primary care with the aim to determine the potential value of clinical features and diagnostic tests for the diagnosis of HF in primary care and to drive referral to a specialist (Mant, Doust et al. 2009). This work showed that several clinical symptoms (orthopnea, edema, lung crepitations) are associated with a high specificity but low sensitivity and that, conversely, NP measurement is highly sensitive. In the absence of symptoms (namely ankle edema), the suggestion of the authors is to refer the de novo diagnosed heart failure patient to a cardiologist in the presence of NT-proBNP > 620 pg/ml in females and > 390 pg/ml in males. According to the authors, the measurement of NT-proBNP is the most sensitive tool to drive referral to a specialist in the absence of compelling specific HF symptoms (Mant, Doust et al. 2009).

Adherence of prescriptions to guideline recommendations is of key importance to ensure patients an optimal treatment and it has been used in several trials as a measure of the appropriateness of clinical practice (Gustafsson and Arnold 2004, Dahlstrom, Hakansson et al. 2009, Maggioni, Anker et al. 2013). It has been reported that more than 50% of acute HF admissions are preventable and under-treatment is one of the leading factors in this regard (Gustafsson and Arnold 2004). In a large, prospective observational survey named MAHLER, conducted in six European countries, it was shown that adherence to HF therapy in symptomatic HF patients is a strong independent predictor of reduced cardiovascular hospitalization rate in daily clinical practice (Komajda, Lapuerta et al. 2005). In addition, although not in HF patients, a paper recently published in Circulation with the title “Doing the right things and doing them the right way” shows that in patients with an acute coronary syndrome there was a significant association between hospitals’ composite guideline adherence rates and unadjusted in-hospital mortality. For every 10% increase in composite adherence at a center, the patient’s in-hospital mortality odds ratio fell by a corresponding 39%. Similarly, for every 10% increase in appropriate dosing at a center, the patient’s in-hospital mortality odds ratio fell by a corresponding 18% (Mehta, Chen et al. 2015).

Taken together, all these observations suggest that optimizing HF treatment is impactful for patients and that referral of selected CHF patients from primary care physicians to specialists

[redacted]

might be beneficial to improve adherence of drug treatment to ESC guideline recommendations, ultimately leading to a better clinical outcome.

1.2 Purpose

The purpose of the present study is to assess if a referral of clinically stable CHF patients with reduced ventricular ejection fraction (≤ 40%) with NT-proBNP levels ≥ 600 pg/ml to a specialist (cardiologist) will lead to treatment optimization, defined as adherence to the treatment recommendations according to the ESC guidelines (McMurray, Adamopoulos et al. 2012). In addition, data obtained in this study will be used to describe demographic, clinical (including NT-proBNP levels) and treatment characteristics of CHF patients who are managed in the primary care setting across Europe. A patient will be judged as being clinically stable when in the opinion of the primary care physician no change of the patient's pharmacological or device treatment for HF is necessary and no change of HF-treatment has been performed within the last 3 months prior to enrollment in the study.

2 Study objectives and endpoints

2.1 Primary objective(s)

To assess if NT-proBNP measurement-guided cardiologist-referral of CHF patients, who are currently judged by their primary care physician as being clinically stable*, leads to optimization of HF treatment, defined as adherence[#] to level I-A treatment recommendations of the current[§] ESC guidelines for the treatment of HF.

***Note:** Within this study, clinically stable patients are defined as those patients, who by the judgement of their primary care physician currently do not require and, in the last 3 months prior to the baseline visit have not had, any change in their pharmacological or device treatment of HF.

[#]**Note:** Adherence to the recommendations of the ESC guidelines within this study is defined as the prescription of all HF specific drugs with level I-A recommendation for a given patient's clinical status at a dose > 50% of the recommended daily dose.

[§]**Note:** Current ESC guidelines are those which are in force on the date the patient signs the informed consent form.

2.2 Secondary objective(s)

- To describe the baseline demographic and clinical characteristics, as well as pharmacological and device treatment of CHF patients managed in the primary care setting (in the total population of enrolled patients and also sub-grouped into different European country and patient characteristics clusters).
- To assess in clinically stable patients the impact of patients' key baseline characteristics on the cardiologists' and primary care physicians' prescription practice for HF treatment and the adherence of these treatment choices to the recommendations of the current ESC guidelines.

[redacted]

- To describe the blood levels of NT-proBNP in CHF patients managed in the primary care setting.
- To describe the proportion of CHF patients managed in the primary care setting considered as being clinically stable according to the above definition (Section 2.1).
- To describe local prescription practice of cardiologists for the treatment of clinically stable CHF patients with NT-proBNP levels ≥600 pg/ml.
- To describe local prescription practice and decision making of primary care physicians for the treatment of clinically stable CHF patients with NT-proBNP levels ≥600 pg/ml.
- To characterize how treatment optimization, defined as prescription of treatment regimens adherent to the recommendations of the ESC guidelines affects NT-proBNP levels in clinically stable CHF patients with baseline NT-proBNP levels ≥ 600 pg/ml.
- To assess the baseline health-related quality of life (QoL) in CHF patients and describe the temporal course of QoL after specialist referral in clinically stable CHF patients with NT-proBNP ≥ 600 pg/ml by means of EuroQol EQ-5D and KCCQ questionnaires.

[redacted]

2.4 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

OBJECTIVE	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure	Stat Analysis Section
Primary		
To assess if NT-proBNP measurement-guided cardiologist-referral of CHF patients, who are currently judged by their primary care physician as being clinically stable, leads to optimization of HF treatment, defined as adherence to level I-A treatment recommendations of the current ESC guidelines for the treatment of HF.	**Title**: Change of the proportion of clinically stable patients whose therapy regimen adheres to ESC guideline recommendations before and after specialist referral. **Description**: Assessment of patients' treatment regimen with respect to ESC guideline adherence at baseline (Visit 1) and after referral to a specialist (visit 2); the change between both visits will be calculated to reflect the proportion of patients for whom optimization was deemed necessary and implemented. For definitions of clinically stable patients and adherence to current ESC guidelines see Section 2.1. **Units of Measure**: Bivariate absolute and relative frequency distributions including 95%-confidence intervals. **Time Frame**: Baseline, Visit 2	Section 9.4

[redacted]

OBJECTIVE	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure	Stat Analysis Section
Secondary		
To describe the baseline demographic and clinical characteristics, as well as pharmacological and device treatment of CHF patients managed in the primary care setting (in the total population of enrolled patients and also sub-grouped into different European country and patient clusters).	**Title**: Demographics Description: Age, gender, race, living conditions, employment status, smoking status, geographical regions, health insurance status, educational level **Title**: Clinical features **Description**: Duration of HF, primary etiology of HF, HF-related hospitalizations in the previous 12 months prior to baseline and during the study, cardiovascular and non-cardiovascular comorbidities **Title**: Pharmacological / device treatment of HF Description: previous and concomitant compound, dose and frequency of administration, device type, duration of treatment **Units** (for all above, as appropriate/applicable): Absolute and relative frequency distributions, descriptive statistics for quantitative data. **Time frame** (for all above): Baseline (Visit 1), Visit 2 and Visit 3	Section 9.2 Section 9.3
To assess in clinically stable patients the impact of patients' key baseline characteristics on the cardiologists' and primary care physicians' prescription practice for HF treatment and the adherence of these treatment choices to the recommendations of the current ESC guidelines.	**Title:** Proportion of clinically stable patients for whom the cardiologist and/or primary care physician optimizes treatment (i.e. prescribes a treatment regimen adherent to ESC guideline recommendations) post referral, stratified according to key baseline characteristics **Description**: For patients who enter the prospective period of the study the post-referral treatment choice of cardiologists and/or primary care physicians will be documented; for patients, for whom the cardiologist and/or primary care physician chose to prescribe a novel HF treatment, the treatment will be assessed, if it fulfills the definition of adherent to ESC guideline recommendation. The proportion of patients for whom an ESC guideline adherent treatment was de novo prescribed will be assessed stratified according to anamnestic (e.g. duration of HF, previous treatment of HF, presence of cardiovascular/ metabolic/ pulmonary comorbidities), demographic (e.g. sex, race, smoking status) and NT-proBNP level categories (e.g. 600 -799 pg/ml, 800 – 999 pg/ml, 1000 – 1200 pg/ml, > 1200 pg/ml). **Units**: Absolute and relative frequency distributions. **Time frame**: Visit 2 and Visit 3	Section 9.3
To describe the blood levels of NT-proBNP in CHF patients managed in the primary care setting	**Title**: NT-proBNP **Description**: NT-proBNP levels (pg/ml) will be measured at baseline in all consecutive patients who satisfy the inclusion and exclusion criteria. Measurements are performed on-site by means of a handheld device provided for the purposes of the study. **Units**: Descriptive statistics for quantitative data, absolute and relative frequency distributions in clinically stable and unstable CHF patients	Section 9.5.3

[redacted]

OBJECTIVE	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure	Stat Analysis Section
	Time frame: One measurement in all consecutive patients at baseline (Visit 1)	
To describe the proportion of CHF patients managed in the primary care setting considered as being clinically stable according to the above definition.	**Title**: Proportion of clinically stable patients **Description**: Clinically stable patients in this study are defined as those patients for whom the primary care physician does not see a necessity (based on signs and symptoms of HF) to change the current pharmacological and/or device treatment of HF and who have been on stable pharmacological and/or device treatment for HF for at least 3 months prior to inclusion. **Units**: Absolute and relative frequency distribution **Time frame**: Baseline (Visit 1)	Section 9.2
To describe local prescription practice of cardiologists for the treatment of clinically stable CHF patients with NT-proBNP levels ≥600 pg/ml.	**Title**: Description of cardiologist prescription practice per country/region **Description**: The cardiologists' suggestions for pharmacological and/or device therapy for the treatment of clinically stable CHF patients (definition see Section 2.1) will be documented and assessed by means of descriptive statistical measures stratified by country/region **Units**: Descriptive statistics, absolute and relative frequency distribution **Time frame**: Visit 2	Section 9.4
To describe local prescription practice and decision making of primary care physicians for the treatment of clinically stable CHF patients with NT-proBNP levels ≥600 pg/ml.	**Title**: Description of primary care physicians' prescription practice per country/region **Description**: For clinically stable CHF patients (definition see Section 2.1) the primary care physicians' prescription of pharmacological and device treatment for HF will be documented prior to (at baseline) and post cardiologist-referral (Visit 2 and Visit 3). At the post-referral visit the degree of implementation of cardiologist-recommendations and the medical decision making (e.g. reasons for non-implementation) will be documented. The primary care physicians' prescriptions will be assessed by means of descriptive statistical measures stratified by country/region. **Units**: Descriptive statistics, absolute and relative frequency distribution **Time frame**: Baseline (Visit 1), Visit 2 and Visit 3	Section 9.4
To demonstrate that treatment optimization, defined as prescription of treatment regimen adherent to the recommendations of the ESC guidelines will lead to clinically relevant decrease of NT-proBNP levels in	**Title**: NT-proBNP levels in clinically stable patients at Visit 3 **Title:** Change of NT-proBNP levels in clinically stable CHF patients with and without treatment optimization at Visit 2 **Description**: At the Visit 3 (end of study) NT-proBNP will again be assessed in clinically stable CHF patients with baseline NT-proBNP levels ≥ 600 pg/ml. Thus, for those patients two NT-proBNP measurements will be available: at baseline and at visit 3. The individual change of NT-proBNP between both time points will be assessed in accordance to the patients' treatment history during the study, i.e. baseline HF treatment and therapeutic decision taken at Visit 2.	Section 9.5.3

[redacted]

OBJECTIVE	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure	Stat Analysis Section
clinically stable CHF patients with baseline NT-proBNP levels ≥ 600 pg/ml.	**Units**: Descriptive statistics for quantitative data, absolute and relative frequency distributions for treatment history subgroups **Time frame**: Baseline (Visit 1) and Visit 3	
To assess the baseline health-related quality of life (QoL) in CHF patients and describe the temporal course of QoL after specialist referral in clinically stable CHF patients with NT-proBNP ≥ 600 pg/ml	**Title**: Change of EQ-5D total and individual sub-scores between Visit 3, Visit 2 and baseline **Title**: Change in KCCQ total and individual sub-scores between Visit 3, Visit 2 and baseline **Title**: Baseline EQ-5D total and individual sub-scores **Title**: Baseline KCCQ total and individual sub-scores **Description**: At baseline (all patients) and at Visit 2 and Visit 3 (only patients who have entered the prospective period of the study, i.e. clinically stable patients with a NT-proBNP level ≥ 600 pg/ml) will be asked to fill out the EuroQol 5D (EQ-5D) and Kansas City Cardiomyopathy Questionnaire (KCCQ) – two quality of life (QoL) questionnaires validated for HF. **Units:** Mean scores, Mean change in scores/sub-scores, absolute and relative frequency distributions of QoL responders (in accordance to the patients' therapeutic regimens at baseline and after specialist referral) **Time frame**: Baseline (Visit 1) and Visit 2 and Visit 3	Section 9.5.1

[redacted]

[redacted]

3 Investigational plan

3.1 Study design

This is an international, prospective, low-interventional study enrolling patients with chronic heart failure with reduced ejection fraction (LVEF ≤ 40%) who are managed in the primary care setting across Europe. The study comprises three visits over a period of maximum 10 months. Enrollment is planned to last 24 months.

At baseline (**visit 1**) for all consecutive patients, who satisfy the inclusion and exclusion criteria, the demographic and clinical characteristics, their current therapy regimen for the treatment of HF, any concomitant medication and their baseline QoL (EQ-5D and KCCQ questionnaires) will be documented. At this visit, after the investigator documents his/her decision whether the patient is considered being clinically stable*, all patients (clinically stable and not stable) will have a blood test for assessing NT-proBNP levels.

Only patients who are considered being clinically stable* by the investigator and who show NT-proBNP blood levels ≥ 600 pg/ml will enter the prospective period of the study.

Patients, who do not fulfill these criteria, i.e. are either not meeting the above definition of clinical stability or who show NT-proBNP levels < 600 pg/ml will not continue further into the study and will have their end-of study documentation at the baseline visit.

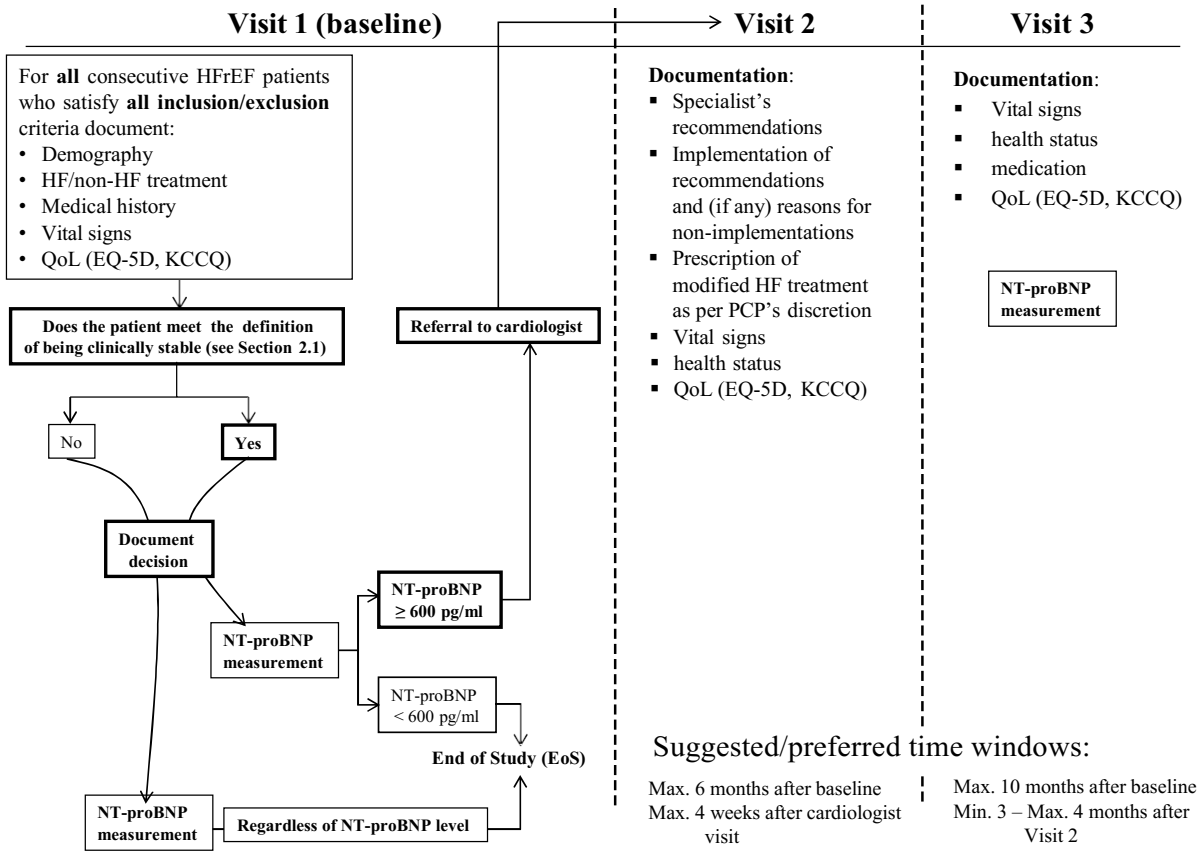
Clinically stable patients with NT-proBNP levels ≥ 600 pg/ml will be referred to a cardiologist for evaluation of their HF treatment. After the referral visit to the specialist's office, the patient will return within a suggested time window of up to 4 weeks after the cardiologist visit to the primary care physician for **visit 2**. During visit 2 the primary care physician will evaluate and record the recommendations provided or treatment changes introduced by the specialist and will make and record his/her decision on the patient's future HF treatment. There is no minimal visit time window for the timing of visit 2, as referral policies differ between different European countries and healthcare systems. However, visit 2 should be performed no later than 6 months after the baseline visit. Within this time frame, the exact timing will be managed by the primary care physician according to his/her practice and local organizational models.

The patients in the prospective period will have a final visit (**visit 3**), that is scheduled to occur at least 3 months but preferably no more than 4 months after visit 2, i.e. maximum 10 months after the baseline visit. During visit 2 and visit 3, the patients will be asked to fill out two QoL questionnaires again (EQ-5D and KCCQ) and a final NT-proBNP measurement will be obtained.

***Note:** Within this study, clinically stable patients are defined as those patients, who by the judgement of their primary care physician currently do not require and, in the last 3 months prior to the baseline visit have not had, any change in their pharmacological or device treatment of HF.

[redacted]

Figure 3-1 Study design



3.2 Rationale for study design

This is an international, prospective, low-interventional study which utilizes a biomarker test (blood NT-proBNP measurement) as a clinical tool for a referral decision from a primary care physician to a cardiologist. A specific treatment does not apply. The primary objective of the study is to assess if a cardiologist referral guided by measurements of NT-proBNP in patients who, in the judgement of the primary care physician, do not require modifications of their HF treatment leads to treatment optimization in these patients, and potentially to better clinical outcomes. As a cut off for the identification of clinically stable patients who could benefit from treatment optimization, an NT-proBNP level of at least 600 pg/ml was chosen (see below). An additional aim is to collect observational data on CHF patients with reduced rejection fraction treated in a primary care setting across Europe and physicians' choices for the treatment of these patients.

Data obtained in Sweden (unpublished, data on file) as well as others (Doust, Pietrzak et al. 2005, Fonarow, Peacock et al. 2007, Kim and Januzzi 2011) show that elevated NT-proBNP is a meaningful predictor of the outcome in HF patients. In fact, elevated NT-proBNP has a similar predictive validity on mortality and cardiovascular events as traditional outcome predictors in HF (Sachdeva, Horwich et al. 2010). Considering that NT-proBNP elevation is a marker reflecting increasing wall stress in the failing heart, and it represents a predictor of

poor outcome and can be assessed easily and objectively in the primary care physician setting, we chose NT-proBNP (akin to the primary care physician's subjective assessment of the patients' clinical stability) as an objective criterion for selecting patients who will be followed prospectively. The selection of the cut-off value for NT-proBNP (600 pg/ml) was based on data obtained in the primary care setting in Sweden (unpublished, data on file). Thus, this cut-off for entering the prospective period of the study, albeit set arbitrarily, should be seen in the context of selecting patients, which are rendered stable by their primary care physician and thus would otherwise not be considered for HF-therapy optimization, however suffer from at least moderate degree of HF-derived cardiac wall stress and therefore bear increased risk of poor clinical outcome.

Supporting this assumption, work by Mant and colleagues suggests that even in the absence of clinical symptoms of HF, undiagnosed patients who show NT-proBNP levels higher than 600 pg/ml could benefit from referral to a cardiologist for further diagnostic evaluation (Mant, Doust et al. 2009).

Based on the literature, no clear guidance could be obtained, if NT-proBNP levels higher or lower than the chosen cut-off would be better selection factors when considering also other influencing factors, e.g. demographic or clinical/anamnestic factors. For instance, differential thresholds regarding gender, country of residence (different healthcare systems) or clinical factors (e.g. comorbidities) could be considered, however the impact of these criteria on NT-proBNP and the numerical magnitude of respective cut-offs are still a matter of debate in the scientific community and indicate the unmet need for further research on this topic. Furthermore, the practical implication of such a differential threshold approach would result in very high level of complexity and too strong guidance on the investigators, could in turn influence the observational nature of the study in an untoward way.

Thus, under the above considerations, and the fact that major, recent clinical studies in CHF have also utilized 600 pg/ml as a selection criterion cut-off for eligible patients (Zannad, McMurray et al. 2011, McMurray, Packer et al. 2014) indicates that the here chosen NT-proBNP cut-off of 600 pg/ml for all patients offers a plausible and robust benchmark for the selection of clinically stable patients who may enter into the prospective period of the study. The NT-proBNP measurements in this study will be performed by means of the same validated procedure in all sites involved, thus assuring comparability between individuals and sites. The chosen cut-off seems to offer the best balance between sensitivity and specificity, mitigates risks for errors during the conduct of the study and still allows for assessment of the impact of different demographic and clinical factors that can be addressed during the statistical analysis of the data.

To achieve the study objectives, i.e. to understand the CHF treatment practices in a European real life setting in clinically stable CHF patients with elevated NT-proBNP levels, data on local prescription practices will be observed and assessed by descriptive methods. The observational data collection methods mitigate the risks for introducing a selection bias, e.g. due to therapeutic, demographic or health-economic factors. Therefore, the chosen design, where a diagnostic test and the referral to a cardiologist are the only stipulated procedures and patient data and data on local treatment practices are collected in an observational manner is best suitable to achieving the study's objectives.

[redacted]

Different study protocol package submission pathways and local endorsement processes apply for such low-interventional clinical studies with a diagnostic procedure (such as the NT-proBNP measurement) depending on country or even investigational site level. Thus, to allow for a common standard of robust data collection, reporting and analysis, the framework of GCP was chosen as the most stringent and harmonized data handling and documentation practice.

The time-actual version of the ESC guidelines for the treatment of HF will be chosen as European reference guideline to which the local prescription practices in the primary care setting will be compared. This means, that the version of the ESC guidelines that is in force at the time when the patients signs the informed consent for participating in this study will be considered as the reference guideline for the analysis of the respective patient's data. The patient population will be described in more detail in the Section 4 below.

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

Not applicable. The study protocol does not stipulate any treatment regimen. The primary care physician's choice of treatment at baseline and after cardiologist referral will be observed, documented, reported by the primary care physician and analyzed. The primary care physicians are advised to follow their local clinical routine, taking the local authorization status of any prescribed treatment into account.

3.4 Rationale for choice of comparator

Not applicable.

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

The risk to subjects in this trial will be minimized by compliance to the eligibility criteria. Blood sampling for NT-proBNP measurements will be performed at the baseline visit and at Visit 3 (for patients who enter the prospective period of the study), which bears minimal risks for the patient, associated with the sampling procedure (venous puncture). Other study procedures are observational, i.e. the investigators should follow and document their local clinical routine for the treatment and follow-up of patients with CHF. There is no investigational medicinal product and no drug/device treatment that is required by the protocol. Therefore the risks associated to this study, besides those associated to the venous blood sampling procedure, are comparable to those in a usual primary care setting.

4 Population

The study population will consist of adult (≥ 18 years) male and female patients with chronic heart failure with reduced ejection fraction (LVEF ≤ 40%) who are currently managed in a primary care setting in sites across Europe. Provided the below inclusion and exclusion

[redacted]

criteria are met, all consecutive CHF patients at a given site will be documented and will be subject to NT-proBNP measurement at baseline. Prior to measuring NT-proBNP at baseline, the physician must provide his/her judgement, whether the patient is considered as clinically stable based on the definition provided in Section 2.1. Patients who do not meet the definition of being clinically stable at baseline and/or patients who show NT-proBNP levels < 600 pg/ml at baseline will not enter the prospective period of the study, but their baseline information will be documented. Patients who enter the prospective period of the study, as defined as clinically stable patients with NT-proBNP levels ≥ 600 pg/ml will be referred to a cardiologist and will return to the site 2 more times (Visit 2 and Visit 3) for follow-up documentation.

It is planned to enroll a total of 4,000 CHF patients of which approximately 2,400 are estimated to enter the prospective period (are considered clinically stable and show NT-proBNP levels ≥ 600 pg/ml). The recruitment will be regarded as completed once approximately 2,400 patients have entered the prospective period irrespectively how many patients have been enrolled totally.

4.1 Inclusion criteria

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

1. Willing and able to provide written informed consent and accept study procedures and time schedule.
2. Age ≥ 18 years.
3. Patients suffering from chronic heart failure (the heart failure diagnosis must have been made or confirmed by a cardiologist and/or hospital physician at any time in the patient's medical history).
4. Patients with reduced ejection fraction (≤ 40%) as confirmed at any time point in the patient's medical history.

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 investigational drugs either within 5 half-lives of enrollment, or within 30 days, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
2. Major surgery in the last 3 months prior to baseline or planned major surgery or cardiac intervention during the study.
3. Cancer or other significant co-morbidities implying that the patient's condition is unstable.
4. Comorbidities that can be associated with elevated natriuretic peptide (NP) levels: renal insufficiency, (eGFR < 25 ml/min/1.73 m² calculated according to MDRD formula), recent (less than 3 months) cerebral trauma or recent (less than 3 months)

[redacted]

cerebrovascular incident, novel diagnosis or acute exacerbation of COPD within the last 3 months.

5. Patients who are primarily managed and regularly followed-up by a cardiologist for their HF
6. Highly frail patients whose estimated lifespan due to comorbidities by the judgement of the investigator is less than 6 months.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Not applicable. No treatment is stipulated by this protocol.

The patients will receive the treatment that their primary care physician has decided to prescribe for their disease. Upon referral to the cardiologist the treatment modification is entirely in the discretion of the primary care physician. The protocol also gives no recommendations to cardiologists and it is planned to only observe the common medical practice.

5.1.2 Additional treatment

Not applicable.

5.2 Treatment arms

Not applicable.

5.3 Treatment assignment and randomization

Not applicable. This is a single arm study without randomization. No treatments are stipulated by this protocol – patients' HF and non-HF treatments will be observed throughout the study. The patients' treatment is entirely in the discretion of the primary care physicians (investigators).

5.4 Treatment blinding

Not applicable. No blinding of patients or investigators is performed within this study.

5.5 Treating the patient

The treatment within this study is not stipulated by the protocol but will be merely documented and observed. The patients' treatment (HF and non-HF therapy) is entirely in the discretion of the investigator. The investigator is not obliged to follow the cardiologist's recommendations.

[redacted]

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number as given by the investigator using the CRF system.

5.5.2 Dispensing the study drug

Not applicable.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Not applicable.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Not applicable. There is no guidance regarding the patients' treatment (including any dose adjustments) stipulated by this protocol.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Not applicable.

5.5.6 Rescue medication

Not applicable.

5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered 12 months before the patient was enrolled into the study, at the time of enrollment and during the study must be recorded in the CRF.

5.5.8 Prohibited medication

Not applicable. There is no guidance regarding the patients' treatment (including any dose adjustments) stipulated by this protocol.

The present study aims to observe local treatment routine and does not stipulate a certain treatment nor are any treatments prohibited. Physicians are advised to follow their clinical routine for the treatment of patients with CHF.

[redacted]

5.5.9 Emergency breaking of assigned treatment code

Not applicable.

Study Completion and Discontinuation

5.6 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last performed visit.

Throughout the study, and beyond completion of the study, the patient's treatment is entirely in the discretion of the investigator, therefore no study and post-study treatments are stipulated by this protocol.

5.6.1 Discontinuation of Study Treatment

Not applicable.

5.6.2 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/her consent and record this information.

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 Table 6-1.

5.6.3 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw from the study, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent process or later in the study and documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc..

[redacted]

5.6.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to practical issues, 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 withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator 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

The study comprises 3 visits: baseline (Visit 1), Visit 2 (recommended max. 6 months after baseline), Visit 3 (recommended at least 3 months and preferably not later than 4 months after Visit 2; max. 10 months after baseline). At baseline (Visit 1) all consecutive CHF patients who satisfy all inclusion and exclusion criteria should be documented and should complete the QoL questionnaires. At this visit, the investigator will assess whether the patient's status is considered clinically stable (as defined in Section 2.1) and document his/her decision. Thereafter all patients will undergo blood-sampling for on-site NT-proBNP measurement. Only patients considered clinically stable and with NT-proBNP levels ≥ 600 pg/ml will be referred to a cardiologist for evaluation of treatment optimization. After the visit to the cardiologist, but no later than 6 months after the baseline visit, the patient should return to the investigator's office for Visit 2. At Visit 2, the patient should complete the QoL questionnaires and the cardiologist's recommendations will be reviewed and documented by the investigator; at this visit, the investigator should document, if the cardiologist's recommendations or changes for the patient's HF-treatment will be followed or continued, respectively. The investigator should provide reasons if the recommendations are not followed and document the prescribed HF treatment. At Visit 3, maximally 10 months after baseline, but no earlier than 3 months after Visit 2, the patient should return for the final visit, where clinical and QoL outcomes will be documented and thereafter the patient will undergo blood sampling for measurement of NT-proBNP levels.

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

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

[redacted]

Table 6-1 Assessment schedule

Visit number	Visit 1	Visit 2	Visit 3
Time of Visit and recommended visit windows	**Baseline**	**After referral** (max. 6 months after baseline)	**Min. 3 months, max 4 months after visit 2** (max. 10 months after baseline)
Informed consent	X		
Inclusion/exclusion criteria	X		
Demographic and clinical history (incl. diagnostic and therapeutic procedures)	X	X [1]	X [1]
Height	X		
Body weight	X		X [1]
Physical examination incl. NYHA-Status and vital signs	X	X [1]	X [1]
Observation of ongoing drug/ non-drug treatment for HF	X	X [1]	X [1]
Observation of relevant laboratory tests, as available per routine care	X	X [1]	X [1]
EQ-5D questionnaire	X	X [1]	X [1]
KCCQ questionnaire	X	X [1]	X [1]
Assessment and documentation of clinical stability of patient (as per Section 2.1)	X		
NT-proBNP assessment	X		X [1]
Referral to cardiologist [1]	X [1]		
Recording of specialist advice/prescription on drug/ non-drug treatment modification [1]		X [1]	
Prescription and documentation of revised treatment in the discretion of primary care physician [1]		X [1]	
Observation of comorbidities and their changes during the study	X	X [1]	X [1]
Adverse events	X	X [1]	X [1]
Report adverse drug reactions to any medication and incidents with medical devices as per local regulations	X	X [1]	X [1]
[1] Applies only for patients who enter the prospective period, i.e. clinically stable patients with NT-proBNP ≥ 600 pg/ml			

[redacted]

6.1 Information to be collected on screening failures

Not applicable.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients/subjects include: year of birth, age, sex, race, living conditions, employment status, education level and smoking status, HF etiology, medical history/current medical conditions that were present before signing informed consent where possible, diagnoses and not symptoms will be recorded. Furthermore, where allowed by local laws and regulations, information on health insurance status will be collected. In addition, HF-hospitalization history and emergency room (ER) admissions due to HF over the last 12 months prior to baseline will be recorded.

The investigator will document for all patients their current HF treatment, including drug- and non-drug treatments, as well as any concomitant medication for non-HF indications.

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.

At baseline all patients will be asked to complete two QoL questionnaires (EQ-5D and KCCQ).

Thereafter the investigator will document if he/she sees the patient as being clinically stable, i.e. the patient currently does not require and, in the last 3 months prior to the baseline visit has not had, any change in his/her pharmacological or device treatment of HF.

All patients will have a venous blood sample taken for on-site measurement of NT-proBNP; please note that this measurement should only be performed after the decision regarding the clinical stability of the patient's status is made and documented.

Only patients considered clinically stable as per above definition by the investigator and with NT-proBNP levels ≥ 600 pg/ml will be referred to a cardiologist for evaluation for treatment optimization.

Patients, who are considered not clinically stable according to the above definition or show NT-proBNP levels < 600 pg/ml will not continue in the prospective period of the study – i.e. only baseline information will be documented for these patients.

6.3 Treatment exposure and compliance

Not applicable. No treatment is stipulated by the protocol.

6.4 Efficacy

Not applicable. There are no efficacy endpoints within the objectives of this study.

[redacted]

6.5 Safety

There are no safety endpoints within the objectives of this study and no study medication. Any adverse event will be recorded in the CRF after the patient has provided his/her informed consent, including adverse events that are related to study procedures (e.g. NT-proBNP assessments). In addition, the below variables, if available, will be documented at baseline and Visit 2 and Visit 3 (as applicable) to describe the clinical features of the patients. Adverse drug reactions (ADR) shall be reported to the authorities following local laws and regulations (Section 7).

6.5.1 Physical examination

The physical examination is to be performed as per the local routine of the primary care physician. At baseline and at each visit (for patients in the prospective period), the patients' NYHA status as well as signs and symptoms of HF and their severity should be documented.

6.5.2 Vital signs

Vital signs include blood pressure and heart rate measurements. Although the examination is to be performed according to local clinical routine, the following process is recommended: After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured in sitting position three times at 1-2 minute intervals. It is further recommended that a validated automated device or sphygmomanometer with an appropriately sized cuff is used and the measurements are obtained on the non-dominant arm. Individual measurements should be recorded in the patient's file and the mean of the three measurements will be recorded in the eCRF.

6.5.3 Height and weight

Body height shall be documented at baseline; body weight will be documented at baseline and at visit 3. Although the examination is to be performed according to local clinical routine, it is advised that body weight be documented to the nearest 0.1 kg in indoor clothing, but without shoes.

6.5.4 Laboratory evaluations

No central laboratory will be used in this study. The investigator will be asked to document relevant laboratory parameters (hemoglobin, creatinine, potassium, as available within the sites' clinical routine) at each visit, however these assessments are not mandatory or stipulated by the protocol.

The on-site measurement of NT-proBNP will be performed by means of a handheld device using measuring strips. This measurement is described in greater detail in Section 6.6.5.

6.5.5 Electrocardiogram (ECG)

Not applicable. No ECG assessment is requested by the protocol. Sites shall follow their clinical routine for the care of patients with CHF.

[redacted]

6.5.6 Pregnancy and assessments of fertility

Not applicable.

6.5.7 Appropriateness of safety measurements

The study has no safety endpoints. The described assessments (Section 6.5) are common in daily clinical routine in the treatment of patients with CHF and should only be documented if they are available. No treatment is stipulated by the study protocol. However all drug and non-drug therapy should be documented in the eCRF and the investigators should follow local regulations for the spontaneous reporting of adverse drug reactions (ADR, events with causal relationship to any treatment the patient may have, see Section 7).

6.6 Other assessments

6.6.1 Clinician Reported Outcomes

The investigator should document the patients' current NYHA status, as well as any change in the severity of any of the patients' concomitant diseases. This will allow for a standardized evaluation of the patients' health status in patients who enter the prospective period of the study.

6.6.2 Patient Reported Outcomes (PRO)

The impact of the disease per se (in all patients) and of CHF treatment optimization (in patients in the prospective period) on health related quality of life (QoL) will be assessed by the following measures:

- EuroQol EQ-5D (EQ-5D-5L)
- Kansas City Cardiomyopathy Questionnaire (KCCQ)

Both questionnaires are available as validated translations in local language.

The patient should be given sufficient instruction, space, time and privacy to complete the questionnaire. The study coordinator should check the responses to the questionnaire for completeness and encourage the patient to complete any missing responses.

As treatment optimization can affect all derived scores and subscales of both questionnaires, the change from baseline for all measures and scales derived from both questionnaires will be analyzed for patients who enter the prospective period of the study.

For patients who are not clinically stable or show NT-proBNP levels < 600 pg/ml only the baseline QoL will be documented.

The patients' responses shall be entered into the CRF by the investigator. The original questionnaire will be kept with the patient's file as the source document.

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). The investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the patient. If AEs or

[redacted]

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.

6.6.2.1 Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ is a self-administered questionnaire that requires 4-6 minutes to complete. It contains 23 items, covering physical function, clinical symptoms, social function, self-efficacy and knowledge, and Quality of Life (QoL).

6.6.2.2 EuroQol EQ-5D

The EuroQol EQ-5D-5L instrument assesses the current health status of patients. It consists of five domains and one visual analogue scale. This instrument assesses morbidity, self-care, usual activity, pain, and anxiety and depression of patients. The questionnaire requires 3-4 minutes to complete.

6.6.4 Pharmacokinetics

Not applicable.

6.6.5 NT-proBNP measurements

At the baseline visit, all CHF patients will undergo on-site NT-proBNP measurement. This measurement should be obtained after the investigator has made and documented his/her judgement of the patient's clinical stability (as per definition provided in Section 2.1).

The NT-proBNP measurement is a prerequisite for deciding if a patient is eligible to continue in the prospective period of the study; this will only be allowed for clinically stable patients with NT-proBNP levels ≥ 600 pg/ml. Only these patients should be referred to a cardiologist and will return for Visits 2 and Visit 3. At Visit 3, patients who have entered the prospective period will undergo NT-proBNP measurement once again.

The sample must be venous whole blood collected in a container including heparin as a preservative. Other anticoagulants such as EDTA or citrate cannot be used. Once the sample has been collected, it must be tested within 8 hours, without prior cooling or freezing.

The test is performed on-site by means of a portable handheld device that will be provided to the sites by Novartis. The device utilizes disposable test strips for testing NT-proBNP levels. For one measurement at least 150 µl whole blood is required.

Device manuals will be provided with detailed information on sample collection, handling, and performing the measurements. The results will be documented in the eCRF by the study site.

6.6.6 Other biomarkers

Not applicable.

7 Safety monitoring

7.1 Adverse events

An AE is any untoward medical occurrence (i.e., 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 the final visit of the study (Visit 3). Therefore, an AE may or may not be temporally or causally associated with the study procedures.

The occurrence of adverse events should 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, laboratory tests, 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 should 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 patients with the underlying disease. Investigators have the responsibility of managing the safety of individual patients and identifying adverse events. The investigators should follow their local clinical routine and use their laboratory facilities as per their discretion. No safety laboratory assessments are stipulated by this protocol.

All adverse events, including events related to the study procedures (e.g. the blood sampling procedure for the NT-proBNP measurements) should be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them accompanied by the following information:

- the severity grade
    - mild: usually transient in nature and generally not interfering with normal activities
    - moderate: sufficiently discomforting to interfere with normal activities
    - severe: prevents normal activities
- its relationship to the study procedures

[redacted]

- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes an SAE
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); concomitant medication given; non-drug therapy given. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

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 study procedures, the interventions required to treat it, and the outcome.

The Sponsor may request additional information on specific adverse events of interest and may make requests to perform additional diagnostic tests to further assess the event. 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.

Adverse events with a causal relationship to any of the patient's drug or non-drug therapies for any disease shall be reported by the investigator to local authorities as per local regulations.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is any adverse event with the 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

[redacted]

- 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.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.2

7.2.2 SAE and Adverse drug reactions (ADR) reporting

Every SAE, regardless of suspected relationship to the study procedures, occurring after the patient has provided informed consent and until the end of the final study visit (Visit 3) should be recorded in the Adverse Events CRF within 24 hours of awareness.

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. 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.

If the investigator becomes aware of any untoward event for which a causal relationship with any of the patient's medication (and/or medical device) cannot be excluded, the investigator should notify local health authorities and the Marketing Authorization Holder (MAH) of the suspect drug (and/or the manufacturer of the device) by means of a spontaneous report (e.g. Adverse Drug Reaction).

An untoward medical occurrence or Adverse Event suspected by the investigator to have a relationship to any Novartis drug (Adverse Drug Reaction) must be reported to the local Novartis Drug Safety and Epidemiology desk following local processes and regulations. Contact details of the local Novartis Drug Safety and Epidemiology desk such as the telephone and fax number or access to an internet reporting tool are listed in the Investigator Folder provided to each site. When reporting incidents to Novartis the study code (CLCZ696B3402) should be provided to allow event traceability (even so no study medication is under investigation for this project and any applicable Novartis medication should be reported).

7.3 Liver safety monitoring

Not applicable.

7.4 Renal safety monitoring

Not applicable.

7.5 Reporting of study treatment errors including misuse/abuse

Not applicable as no study treatment is provided. In cases of drug/device misuse and abuse local regulations, processes and legislation on reporting should be followed.

7.6 Pregnancy reporting

Not applicable. Local laws and regulations for reporting adverse drug reactions should be followed.

[redacted]

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a study center initiation visit or at an Investigator's meeting, a Novartis representative will review the protocol and eCRFs with the Investigators and their staff. During the study, the field monitor will visit the study center regularly to check the completeness of patient records, the accuracy of entries in the eCRFs, the adherence to the protocol and to GCP and the progress of enrollment. Key study personnel must be available to support the field monitor during these visits.

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, 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 ICF signed by the patient (a signed copy is given to the patient).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables.

Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to US CFR 21 Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. During data entry, data is checked for completeness and correctness via automatic plausibility checks. In case of data discrepancies an appropriate error message will be shown asking the Investigator to confirm or correct data. The Investigator must certify by electronic signature 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 CRO data management working on behalf of Novartis or Novartis staff will review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. Concomitant medications and procedures and non-drug therapies entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history and adverse events will be coded using the Medical

[redacted]

dictionary for regulatory activities (MedDRA) terminology. Local laboratory data regarding hemoglobin, creatinine and/or potassium will be entered into the eCRF if available within the sites' clinical routine. 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 made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

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

Details of the planned statistical analysis will be described in detail in a separate statistical analysis plan.

9.1 Analysis sets

Analysis of baseline variables will be carried out on all patients who signed the study information consent (Enrolled Set).

Analysis regarding the prospective period of the study will be carried out on all patients entering into this study period – the respective patient set will be labeled Follow-up Set.

9.2 Patient demographics and other baseline characteristics

Summary statistics will be provided for demographics and other baseline characteristics described in Section 6.2. Additionally, age groups (< 65, ≥ 65 to < 75, ≥ 75 to < 85, ≥ 85 years) and BMI calculated as weight (kg) / (height (m))^2 will be displayed. Classification of patients as "clinically stable" will be provided.

Continuous variables will be summarized using n, mean, median, standard deviation, minimum, maximum, and categorical variables will be summarized using frequency and percentage.

Baseline characteristics will be displayed for all patients in the Enrolled Set, stratified by the variable "inclusion into the prospective period of the study".

9.3 Treatments

No study treatment will be provided in this trial.

[redacted]

Prior and concomitant medication will be presented separately for medications due to HF and other medication. Concomitant medications are defined as any medications administered at or after the enrollment date into the study, otherwise the medication is defined as prior.

The assessment of the patient's treatment at every visit with respect to the adherence to the time-actual ESC guidelines will be provided (definition see Section 2.1).

Separate summaries will be provided for all treatment changes advised by the cardiologist and the implementation of these changes to the actual treatment of the patient by the primary care physician.

Additionally, statistical models might be considered for analyzing associations between ESC guideline adherence of treatment regimens and possible covariates. Such models will be described in detail in the Statistical Analysis Plan.

The analysis of the patients' treatment will be performed for all patients in the Enrolled Set (where applicable) in the Follow-up Set. All treatment analyses will additionally be performed stratified by country/region.

9.4 Analysis of the primary variable(s)

The primary objective in this study is to assess if NT-proBNP measurement-guided cardiologist-referral of CHF patients, who are currently judged by their primary care physician as being clinically stable, leads to optimization of HF treatment, defined as adherence to level I-A treatment recommendations of the current ESC guidelines for the treatment of HF. Therefore the aim of the primary analysis is to estimate the proportion of patients switching from a non-ESC guideline recommendations-adherent HF treatment at baseline to a guideline-adherent treatment after referral to a cardiologist.

9.4.1 Variable(s)

The variables used for the primary analysis are the assessment of the patient's treatment at baseline (A1) and the assessment of the patient's treatment at visit 2 (A2) with respect to the adherence to the current ESC guidelines.

9.4.2 Statistical model, hypothesis, and method of analysis

The analysis yielding to the primary objective will be performed by estimating the proportion of patients who are switched to an ESC guideline recommendation-adherent regimen after referral to a cardiologist based on all referred patients whose treatment does not adhere to these recommendations. A respective 95%- confidence interval (CI) will be provided for this proportion.

Cross-tabulation between the variables A1 and A2 will be displayed showing further absolute and relative frequencies, including the proportion of patients being treated in accordance to the ESC guideline recommendations already at baseline (i.e. before referral), the proportion of patients receiving ESC guideline-adherent treatment after the referral to the cardiologist and the rate of patients who remain on a therapy regimen that does not adhere to ESC guideline-recommendations after referral over all patients without ESC guideline-adherent treatment. Respective 95%-CIs will be provided for the estimates.

[redacted]

The analysis of the primary endpoint will be performed in the Follow-up Set.

9.4.3 Handling of missing values/censoring/discontinuations

No imputation of missing values will be performed. The analysis of the primary variable will be based on all available cases, i.e. on all patients for whom assessments of treatment before and after cardiologist referral are available. Additionally, proportions based on all patients including missing values for the treatment after referral will be presented.

9.4.4 Sensitivity analyses

In order to detect possible country effects or effects of further subgroups and allow for a site and patient profiling, stratified analyses of the primary endpoint will be performed at least for the following subgroups:

- Country/region cluster information for site
- Sex
- Age groups
- NT-proBNP levels

Please refer for details to the Statistical Analysis Plan.

9.5 Analysis of secondary variables

Analysis of secondary variables will be performed in the Follow-up Set and additionally stratified by the assessment of the treatment before and after referral to a cardiologist (*ESC non-conform/ESC conform*, *ESC non-conform/ESC non-conform*, *ESC conform/ESC conform*, *ESC conform/ESC non-conform*).

9.5.1 Patient reported outcomes

Health related quality of life as measured by the patient reported outcomes EQ-5D-5L and KCCQ.

The KCCQ instrument includes several domains. Only the domains that address HF symptoms and physical limitations will be analyzed. The clinical summary score of KCCQ is computed as the mean of the following available domain scores:

- Physical limitation score
- Total HF symptom score

Minimal clinical improvement according to the KCCQ will defined for each of the two domain scores as an improvement of at least 5 points compared to baseline (Flynn, Lin et al. 2012).

The EQ-5D-5L consists of five domains and one visual analogue scale. This instrument assesses morbidity, self-care, usual activity, pain, and anxiety and depression of patients on a five-point rating scale ranging from *1=no problems* to *5=extreme problems*. A continuous utility index will be derived from these dimensions.

[redacted]

Quantitative outcomes such as KCCQ sub-domains, EQ-5D visual analogue scale and EQ-5D utility index will be displayed in terms of descriptive statistical parameters such as valid n, mean, SD, minimum, median and maximum at each visit.

Furthermore, for visit 2 the change from baseline and for visit 3 the change from baseline and from visit 2 will be calculated and displayed.

In case of ordinal or dichotomous measures such as EQ-5D dimensions and KCCQ response distributions in terms of absolute and relative frequencies will be provided for the single visits.

9.5.2 Safety variables

Adverse events (AEs) will be coded by means of the Medical Dictionary for Regulatory Activities (MedDRA). Incidence rates of AEs and Serious Adverse Events (SAEs) due to study related procedures based on "preferred terms" and "system organ class" will be displayed. Additionally, all AEs will be individually listed.

9.5.3 Biomarkers

NT-proBNP will be collected in all patients at baseline and visit 3 (only for patients who have entered the prospective period). Summary statistics for quantitative and qualitative data will be provided for each visit. The change in NT-proBNP level from baseline to visit 3 will be calculated and presented describing the amount of quantitative change and the number of patients with increase/decrease of NT-proBNP blood level.

[redacted]

9.7 Interim analyses

An interim analysis describing baseline characteristics and data collected at Visit 1 can be performed. Details are described in the Statistical Analysis Plan.

9.8 Sample size calculation

The study is powered to estimate the proportion of patients switching from a non-ESC guideline recommendations-adherent treatment to regimen adhering to these recommendations after referral to a cardiologist based on all patients who at baseline are judged by their primary care physician to be clinically stable and show NT-proBNP levels ≥ 600 pg/ml.

Based on the data from Dahlstrom et al (Dahlstrom, Hakansson et al. 2009), showing that only 20% of patients followed by primary care physician receive both Renin-Angiotensin System inhibitors and beta-blockers at a dose ≥50% of the recommended, we conservatively assume 20% as the percentage of CHF patients that will be treated in accordance to the ESC guidelines (i.e. prescription of any drugs with level I-A recommendation for a given patient's

[redacted]

clinical status at a dose of > 50% of the recommended daily dose) at baseline (Visit 1). In addition, we assume that after referral to a specialist (Visit 2), the proportion will increase to 30% (Maggioni, Anker et al. 2013). Although there are no data in the literature measuring the clinical impact of increasing guideline-adherence of treatment in HF, it has been clearly demonstrated that a 10% increase in acute coronary syndrome is clinically highly significant. In fact, for every 10% increase in guideline-adherence at a hospital center, the in-patient's mortality odds ratio falls by a corresponding 39%. Similarly, for every 10% increase in appropriate dosing, the patient's mortality odds ratio falls by a corresponding 18% (Mehta, Chen et al. 2015).

We further assume that around 25% of patients without ESC guideline recommendations-adherent treatment at baseline (i.e. prior to referral to a cardiologist) will receive optimization (i.e. ESC guideline adherent treatment) of their HF treatment post referral to the cardiologist. This proportion can be estimated with a precision of ± 2% using a 95%-CI by including 1,728 patients into the analysis; for subgroup analyses (e.g. on country level) the range of a 95%-CI increases, however it is still possible to estimate the proportion with a precision of ± 5% for subgroups of 300 patients.

Considering of the above assumptions, a number of 2,160 patients who enter the prospective period of the study (i.e. referral to a cardiologist) is required. It is further assumed, based on unpublished data from chronic heart failure registries (data on file), that at least around 60% of patients treated by primary care physicians will have NT-proBNP levels ≥600 pg/ml at baseline. This in turn leads to the calculation that, in order to obtain 2.160 patients in the prospective period of the study, 3,600 consecutive patients will need to be enrolled for visit 1 (baseline).

Assuming an expected drop-out rate of 10% of patients, 4,000 patients will be enrolled of whom 2,400 will enter into the prospective period.

The sample size calculation was performed with nQuery Advisor version 7.0 'using Table POC0-1.

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed

[redacted]

about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

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

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients/subjects as per local law and regulations. 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 submitted for publication and/or posted in a publicly accessible database of clinical trial results (as applicable).

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients/subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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

11.1 Protocol Amendments

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

12 References

References are available upon request

Calvert, M. J., A. Shankar, R. J. McManus, R. Ryan and N. Freemantle (2009). "Evaluation of the management of heart failure in primary care." Fam Pract 26(2): 145-153.

Cleland, J. G., A. Cohen-Solal, J. C. Aguilar, R. Dietz, J. Eastaugh, F. Follath, N. Freemantle, A. Gavazzi, W. H. van Gilst, F. D. Hobbs, J. Korewicki, H. C. Madeira, I. Preda, K. Swedberg, J. Widimsky, I. o. H. F. P. Committees, e. Investigators. Improvement programme in, management and C. Study Group on Diagnosis of the Working Group on Heart Failure of The European Society of (2002). "Management of heart failure in primary care (the IMPROVEMENT of Heart Failure Programme): an international survey." Lancet 360(9346): 1631-1639.

Crissinger, M. E., K. M. Marchionda and M. E. Dunlap (2015). "Adherence to clinical guidelines in heart failure (HF) outpatients: Impact of an interprofessional HF team on evidence-based medication use." J Interprof Care 29(5): 483-487.

Dahlstrom, U., J. Hakansson, K. Swedberg and A. Waldenstrom (2009). "Adequacy of diagnosis and treatment of chronic heart failure in primary health care in Sweden." Eur J Heart Fail 11(1): 92-98.

Del Ry, S., M. Cabiati and A. Clerico (2013). "Recent advances on natriuretic peptide system: new promising therapeutic targets for the treatment of heart failure." Pharmacol Res 76: 190-198.

Del Ry, S., M. Cabiati and A. Clerico (2014). "Natriuretic peptide system and the heart." Front Horm Res 43: 134-143.

Doust, J. A., E. Pietrzak, A. Dobson and P. Glasziou (2005). "How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review." BMJ 330(7492): 625.

Flint, K. M., L. A. Allen, M. Pham and P. A. Heidenreich (2014). "B-type natriuretic peptide predicts 30-day readmission for heart failure but not readmission for other causes." J Am Heart Assoc 3(3): e000806.

Flynn, K. E., L. Lin, G. W. Moe, J. G. Howlett, L. J. Fine, J. A. Spertus, T. R. McConnell, I. L. Pina and K. P. Weinfurt (2012). "Relationships between changes in patient-reported health status and functional capacity in outpatients with heart failure." Am Heart J 163(1): 88-94 e83.

[redacted]

Fonarow, G. C., W. F. Peacock, C. O. Phillips, M. M. Givertz, M. Lopatin, A. S. A. Committee and Investigators (2007). "Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure." J Am Coll Cardiol 49(19): 1943-1950.

Fonseca, C. (2006). "Diagnosis of heart failure in primary care." Heart Fail Rev 11(2): 95-107.

Gustafsson, F. and J. M. Arnold (2004). "Heart failure clinics and outpatient management: review of the evidence and call for quality assurance." Eur Heart J 25(18): 1596-1604.

Hobbs, F. D., J. Doust, J. Mant and M. R. Cowie (2010). "Heart failure: Diagnosis of heart failure in primary care." Heart 96(21): 1773-1777.

Januzzi, J. L., Jr., R. Sakhuja, M. O'Donoghue, A. L. Baggish, S. Anwaruddin, C. U. Chae, R. Cameron, D. G. Krauser, R. Tung, C. A. Camargo, Jr. and D. M. Lloyd-Jones (2006). "Utility of amino-terminal pro-brain natriuretic peptide testing for prediction of 1-year mortality in patients with dyspnea treated in the emergency department." Arch Intern Med 166(3): 315-320.

Kim, H. N. and J. L. Januzzi, Jr. (2011). "Natriuretic peptide testing in heart failure." Circulation 123(18): 2015-2019.

Komajda, M., P. Lapuerta, N. Hermans, J. R. Gonzalez-Juanatey, D. J. van Veldhuisen, E. Erdmann, L. Tavazzi, P. Poole-Wilson and C. Le Pen (2005). "Adherence to guidelines is a predictor of outcome in chronic heart failure: the MAHLER survey." Eur Heart J 26(16): 1653-1659.

Kuck, K. H., P. Bordachar, M. Borggrefe, G. Boriani, H. Burri, F. Leyva, P. Schauerte, D. Theuns, B. Thibault, R. Document, P. Kirchhof, G. Hasenfuss, K. Dickstein, C. Leclercq, C. Linde, L. Tavazzi and F. Ruschitzka (2014). "New devices in heart failure: an European Heart Rhythm Association report: developed by the European Heart Rhythm Association; endorsed by the Heart Failure Association." Europace 16(1): 109-128.

Maggioni, A. P., S. D. Anker, U. Dahlstrom, G. Filippatos, P. Ponikowski, F. Zannad, O. Amir, O. Chioncel, M. C. Leiro, J. Drozdz, A. Erglis, E. Fazlibegovic, C. Fonseca, F. Fruhwald, P. Gatzov, E. Goncalvesova, M. Hassanein, J. Hradec, A. Kavoliuniene, M. Lainscak, D. Logeart, B. Merkely, M. Metra, H. Persson, P. Seferovic, A. Temizhan, D. Tousoulis, L. Tavazzi and E. S. C. Heart Failure Association of the (2013). "Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry." Eur J Heart Fail 15(10): 1173-1184.

Mant, J., J. Doust, A. Roalfe, P. Barton, M. R. Cowie, P. Glasziou, D. Mant, R. J. McManus, R. Holder, J. Deeks, K. Fletcher, M. Qume, S. Sohanpal, S. Sanders and F. D. Hobbs (2009). "Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care." Health Technol Assess 13(32): 1-207, iii.

Masson, S., R. Latini, I. S. Anand, S. Barlera, L. Angelici, T. Vago, G. Tognoni, J. N. Cohn and F. T. I. Val-He (2008). "Prognostic value of changes in N-terminal pro-brain natriuretic peptide in Val-HeFT (Valsartan Heart Failure Trial)." J Am Coll Cardiol 52(12): 997-1003.

[redacted]

McMurray, J. J., S. Adamopoulos, S. D. Anker, A. Auricchio, M. Bohm, K. Dickstein, V. Falk, G. Filippatos, C. Fonseca, M. A. Gomez-Sanchez, T. Jaarsma, L. Kober, G. Y. Lip, A. P. Maggioni, A. Parkhomenko, B. M. Pieske, B. A. Popescu, P. K. Ronnevik, F. H. Rutten, J. Schwitter, P. Seferovic, J. Stepinska, P. T. Trindade, A. A. Voors, F. Zannad, A. Zeiher, D. Task Force for the, A. Treatment of, C. Chronic Heart Failure of the European Society of, J. J. Bax, H. Baumgartner, C. Ceconi, V. Dean, C. Deaton, R. Fagard, C. Funck-Brentano, D. Hasdai, A. Hoes, P. Kirchhof, J. Knuuti, P. Kolh, T. McDonagh, C. Moulin, B. A. Popescu, Z. Reiner, U. Sechtem, P. A. Sirnes, M. Tendera, A. Torbicki, A. Vahanian, S. Windecker, T. McDonagh, U. Sechtem, L. A. Bonet, P. Avraamides, H. A. Ben Lamin, M. Brignole, A. Coca, P. Cowburn, H. Dargie, P. Elliott, F. A. Flachskampf, G. F. Guida, S. Hardman, B. Iung, B. Merkely, C. Mueller, J. N. Nanas, O. W. Nielsen, S. Orn, J. T. Parissis, P. Ponikowski and E. S. C. C. f. P. Guidelines (2012). "ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC." Eur J Heart Fail 14(8): 803-869.

McMurray, J. J., M. Packer, A. S. Desai, J. Gong, M. P. Lefkowitz, A. R. Rizkala, J. L. Rouleau, V. C. Shi, S. D. Solomon, K. Swedberg, M. R. Zile, P.-H. Investigators and Committees (2014). "Angiotensin-neprilysin inhibition versus enalapril in heart failure." N Engl J Med 371(11): 993-1004.

Mehta, R. H., A. Y. Chen, K. P. Alexander, E. M. Ohman, M. T. Roe and E. D. Peterson (2015). "Doing the right things and doing them the right way: association between hospital guideline adherence, dosing safety, and outcomes among patients with acute coronary syndrome." Circulation 131(11): 980-987.

Parikh, R. and P. J. Kadowitz (2013). "A review of current therapies used in the treatment of congestive heart failure." Expert Rev Cardiovasc Ther 11(9): 1171-1178.

Pruett, A. E., A. K. Lee, J. H. Patterson, T. A. Schwartz, J. M. Glotzer and K. F. Adams, Jr. (2015). "Evolution of biomarker guided therapy for heart failure: current concepts and trial evidence." Curr Cardiol Rev 11(1): 80-89.

Sachdeva, A., T. B. Horwich and G. C. Fonarow (2010). "Comparison of usefulness of each of five predictors of mortality and urgent transplantation in patients with advanced heart failure." Am J Cardiol 106(6): 830-835.

Singh, H., J. C. McGregor, S. J. Nigro, A. Higginson and G. C. Larsen (2014). "Evaluation of collaborative therapy review to improve care of heart failure patients." Am J Manag Care 20(10): e425-431.

Troughton, R. W., C. M. Frampton, H. P. Brunner-La Rocca, M. Pfisterer, L. W. Eurlings, H. Erntell, H. Persson, C. M. O'Connor, D. Moertl, P. Karlstrom, U. Dahlstrom, H. K. Gaggin, J. L. Januzzi, R. Berger, A. M. Richards, Y. M. Pinto and M. G. Nicholls (2014). "Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis." Eur Heart J 35(23): 1559-1567.

Wakefield, B. J., S. A. Boren, P. S. Groves and V. S. Conn (2013). "Heart failure care management programs: a review of study interventions and meta-analysis of outcomes." J Cardiovasc Nurs 28(1): 8-19.

[redacted]

Zannad, F., J. J. McMurray, H. Krum, D. J. van Veldhuisen, K. Swedberg, H. Shi, J. Vincent, S. J. Pocock, B. Pitt and E.-H. S. Group (2011). "Eplerenone in patients with systolic heart failure and mild symptoms." N Engl J Med 364(1): 11-21.

[redacted]