Statistical Analysis Plan – Final Analysis

Study title:	a Prospective evaluation of natRiuretic pEptide based reFerral of CHF patiEnts in pRimary care - PREFER
Indication studied:	Chronic Heart Failure
Sponsor:	Novartis
Study number:	CLCZ696B3402 / NCT02807857
EudraCT number:	2016-000473-20
Phase of study:	Low-interventional study
Author:	[redacted]
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Signatures

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List of abbreviations and definition of terms

Abbreviation	Term
ACEi	Angiotensin converting enzyme inhibitor
AE	Adverse event
ARB	Angiotensin receptor blocker
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CHF	Chronic heart failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EQ-5D	EuroQol five dimensions questionnaire
ESC	European society of cardiology
GFR	Glomerular filtration rate
HF	Heart failure
KCCQ	Kansas City cardiomyopathy questionnaire
LVEF	Left ventricular ejection fraction
MDRD	Modification of diet in renal disease
MedDRA	Medical dictionary for regulatory activities
MRA	Mineralocorticoid receptor blocker
MRI	Magnetic resonance imaging
NP	Natriuretic peptide
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York heart association
PT	Preferred term
QC	Quality control
QoL	Quality of life
SAP	Statistical analysis plan
SDVP	Structure and data validation plan

SOC	System organ class
VAS	Visual analogue scale
WHO	World health organization

Definition of terms

A1: Assessment of the patient's treatment at Visit 1

A2: Assessment of the patient's treatment at Visit 2

A3: Assessment of the patient's treatment at Visit 3

1 Study protocol and scope

This Statistical Analysis Plan (SAP) describes the planned analyses for the final analysis of the low-interventional PREFER study. It is based on the final version 00 of the protocol, dated 15 February 2016.

2 General definitions and procedures

2.1 Software

Statistical analyses will be carried out with the SAS® package (version 9.4 or higher).

2.2 Coding

Concomitant diseases and adverse events (AEs) are coded by means of the Medical Dictionary for Regulatory Activities (MedDRA dictionary), English version (latest version available at the start of coding).

Therapy of heart failure (HF) and concomitant medication will be coded by means of the WHO Drug Dictionary including anatomical therapeutic chemical (ATC) classification up to level 4 and preferred name (latest version at the start of coding).

2.3 Procedures prior to statistical analysis

Prior to the final analysis data cleaning procedures as described in section 2.5 will be performed. Subsequently, an export of the electronic case report form (eCRF) data will be performed providing the source data base for the final analysis.

Thereafter, only the responsible data manager and the project statistician will be privileged to have access to this data base. Any changes to the analyses after the SAP has been finalized will be clearly described in the study report.

After data base closure, the data will be transferred electronically to the statistical software package SAS® data set format for statistical analysis. The SAS® data sets will be considered as source data sets for statistical analysis.

2.4 Reporting standard

An integrated clinical study report in English language according to [redacted] standards will be generated.

2.5 Quality control

Data validation is carried out according to the Structure and Data Validation Plan (SDVP, version 6.0, 20 March 2018). The SDVP defines criteria and responsibilities for general and medical plausibility checks of the data. Prior to the final analysis, a comprehensive cleaning of the available data with respect to the criteria defined in the SDVP is performed. This comprehensive cleaning includes an enforced data and query review aiming to solve any inconsistencies within the data. The quality control includes

checking for completeness, correctness and plausibility, and is carried out by the data management department in cooperation with the responsible medical advisor.

The SAP is consistent with the underlying protocol. If there is a need for deviating substantially from the protocol-defined analysis, this is described in detail. The methods described in this SAP are mandatory for statistical programming.

Quality control (QC) of statistical programming will be performed according to the QC plan, which specifies all planned actions to ensure that the performed analyses are correct, traceable and in line with the planned analysis as specified in the SAP. The QC plan also includes filing of statistical programs, outputs and documentation of QC. It is finalized by the project statistical programmer before the start of any programming activities.

Documentation of QC is filed in the trial master file.

3 Study objectives

3.1 Primary objective(s)

The primary objective of this study is to assess if NT-proBNP measurement-guided cardiologist-referral of chronic heart failure (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.

3.2 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.
- 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
- 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 EQ-5D and KCCQ questionnaires.

[redacted]

4 Essential features of the study design

4.1 Type of study

This is an international, prospective, low-interventional study enrolling patients with CHF 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.

4.2 Study population

According to the protocol, it was planned to enroll a total of 4000 CHF patients of which approximately 2400 are estimated to enter the prospective period (who are considered clinically stable and show NT-proBNP levels ≥ 600 pg/ml). The recruitment was to be regarded as completed once approximately 2400 patients have entered the prospective period irrespectively how many patients have been enrolled totally.

However, it was decided by Novartis to determine the study prematurely, i.e. to stop recruiting and data collection in March 2018: therefore, last patient first visit was on 07 March 2018, last patient last visit on 23 March 2018. This means, that not every subject was able to perform Visit 3 of the study.

Patients/subjects eligible for inclusion in this study had to fulfil all of the following 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 in the patient's medical history).
- Patients with reduced ejection fraction (≤ 40%) as confirmed at any time point in the patient's medical history.

Patients/subjects fulfilling any of the following criteria were not eligible for inclusion in this study.

- 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.
- Major surgery in the last 3 months prior to Baseline or planned 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 < 30 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 by the judgement of the investigator is less than 6 months.

4.3 Study treatment

The patients received the treatment that their primary care physician has decided to prescribe for their disease. Upon referral to the cardiologist the treatment modification was entirely in the discretion of the primary care physician.

4.4 Study schedule

The study comprised 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 satisfied all inclusion and exclusion criteria were to be documented and should complete the QoL questionnaires. At this visit, the investigator assessed whether the patient's status was considered clinically stable (as defined in Section 3.1) and documented his/her decision. Thereafter, all patients underwent blood-sampling for on-site NT-proBNP measurement. Only patients considered clinically stable and with NT-proBNP levels ≥ 600 pg/ml were 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 was 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 were followed or continued, respectively. The investigator should provide reasons if the recommendations were not followed and document the prescribed HF treatment. At Visit 3, not later than 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 were documented. Thereafter, the patient underwent blood sampling for measurement of NT-proBNP levels.

Table 4-1 lists all of the assessments and indicates with an "x" when the visits were performed.

Table 4-1 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	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			

4.5 Measures

4.5.1 Primary measures

The primary effectiveness measure is the adherence (yes/no) of HF treatment to the current ESC guideline [1, 2]. The following measures of HF therapy and concomitant medication will be used for derivation of the primary effectiveness measure:

- Active ingredient

- Single dose and dose unit
- Start and end date

Following the ESC guideline definitions, two levels of guideline adherence will be used for the analysis: adherence with respect to drug types (level 1) and adherence with respect to drug types **and** drug dose (level 2). The exact definitions of both levels of guideline adherence are provided in Table 4-2.

Table 4-2 ESC guideline definitions

Guideline level	Criteria for guideline adherence
Drug types	Treatment with one* ACEi+° or one* ARB+, in combination with one* beta-blocker+ and one* MRA+ for patients with an LVEF ≤ 35% at Visit 1 Treatment with one* ACEi+° or one* ARB+, in combination with one* beta-blocker+ without treatment with an MRA for patients with an LVEF > 35% at Visit 1
Drug type and dose	Guideline adherent with respect to drug types and dosage of all respective guideline drugs ≥ 50% of the recommended target dose #

* exactly one
+ Only drugs with indication for treatment of HF will be considered as according to guidelines. Any use of a drug from the respective class with no indication for HF leads to treatment classified as non-adherent.
° Alternatively: Sacubitril/Valsartan
In case a recommended target dose of a HF medication cannot be defined, the criterion for guideline adherence with respect to drug dose will be considered as fulfilled for this drug (independent from the actual dose)

For identification of the drugs relevant for guideline adherence the following implementations will be used:

- ACEi: ATC texts "ace inhibitors and diuretics", "ace inhibitors, plain"
- ARB: ATC texts "angiotensin ii antagonists and calcium channel blockers", "angiotensin ii antagonists and diuretics", "angiotensin ii antagonists, plain"
- Beta-blocker: ATC texts "alpha and beta blocking agents", "beta blocking agents, non-selective", "beta blocking agents, selective", "beta blocking agents, selective, and thiazides"
- MRA: ATC code C03DA

Table 4-3 describes guideline relevant treatments with indication for HF and provides the respective target doses to be applied for the guideline analyses:

Table 4-3 Recommended target doses used for guideline analyses

Treatment	Recommended total daily target dose (mg)
ACEi	
Benazepril	40
Captopril	150
Cilazapril	10
Enalapril	20
Fosinopril	80
Lisinopril	35
Perindopril	16
Quinapril	80
Ramipril	10
Trandolapril	4
Sacubitril/Valsartan*	194/206*
ARB	
Candesartan	32
Losartan	150
Valsartan	320
Beta-blocker	
Bisoprolol	10
Carvedilol	50
Metoprololsuccinat, Metoprolol	200
Nebivolol	10
MRA	
Eplerenone	50
Spironolactone	50

* Considered as (exactly) one treatment with combined total daily target dose of 400 mg.

The following drugs do not have an indication for HF and will yield the patient being classified as non-adherent: Moexipril (ACEi), Zofenopril (ACEi), Eprosartan (ARB), Irbesartan (ARB), Olmesartan medoxomil (ARB), Telmisartan (ARB), Atenolol (Beta-blocker), Betaxolol (Beta-blocker), and Sotalol (Beta-Blocker).

The HF indication and the daily target dose of any ACEi, beta-blocker, ARB or MRA neither included in this list nor in Table 4-3 but occurring in the data (according to the above described implementations) will be identified separately and confirmed by Novartis.

In case the dose is not given in “total daily dose in mg”, it will be converted respectively.

4.5.2 Secondary measures

EuroQol five dimensions five levels questionnaire (EQ-5D-5L)

The EQ-5D is a non-disease specific, validated and widespread instrument for quantifying the life quality of adult patients. The measure is divided into two distinct sections. The first section includes five rating scales addressing each of five dimensions (mobil-

ity, self-care, usual activity, pain/discomfort, and anxiety/depression). The second section includes a self-rated (global) health status measurement utilizing a vertically oriented visual analogue scale where 100 represents the "best possible health state" and 0 represents the "worst possible health state".

In the current study the EQ-5D-5L version of the questionnaire is used. In this version the extent of problems in each single life quality dimension can be assessed by five levels: no problems, slight problems, moderate problems, severe problems, unability in the respective dimension.

The EQ-5D-5L utility index is derived to summarize the information of the five life quality dimensions. For this, a weighted mean with level- and dimension-specific weights (i.e. a specific value set) is calculated. For this analysis, the EQ-5D-5L value set for the UK (https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation/; Devlin et al., 2016) is used. Weights for each dimension and each level of problem are defined as follows (the weight for the category "no problems" within any dimension is set to 0):

- Mobility:
  - slight: 0.051
  - moderate: 0.063
  - severe: 0.212
  - unable: 0.275
- Self-care:
  - slight: 0.057
  - moderate: 0.076
  - severe: 0.181
  - unable: 0.217
- Usual activities:
  - slight: 0.051
  - moderate: 0.067
  - severe: 0.174
  - unable: 0.190
- Pain/discomfort:
  - slight: 0.060
  - moderate: 0.075
  - severe: 0.276
  - extreme: 0.341
- Anxiety/depression:
  - slight: 0.079
  - moderate: 0.104
  - severe: 0.296
  - extreme: 0.301

The utility index will be calculated as 1 - 0.9675 × ∑(weight of each dimension). Values of this index can range between -0.281 and 1.0 where a higher number indicates a better health status.

Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ is a HF-specific questionnaire and requires on average 4-6 minutes to complete. It covers physical function, clinical symptoms, social function, self-efficacy and

knowledge, and QoL. The following KCCQ domains will be calculated for this study: physical limitation, symptom stability, symptom frequency, symptom burden, self-efficacy, QoL, and social limitation. Each subscore is transformed to a 0–100 scale, with higher score indicating higher level of functioning. A score of 100 represents perfect health whereas a score of 0 represents the worst condition. A clinical summary score is built by the mean of the physical limitation and total symptom scores. The total symptom score is calculated as the mean of the symptom frequency and symptom burden scores. Below are the calculation rules for each score:

- Physical Limitation. Physical Limitation Score = 100*[(mean of questions 1a-f actually answered) – 1]/4
- Symptom stability
    - If question 2 was answered with 6 (=no symptoms over the last 2 weeks) this will be transferred to 3 (=not changed).
    - Symptom stability score = 100* [(Question 2) – 1]/4
- Symptom frequency. Symptom Frequency is computed based on the following standardization:
    - S3 = [(Question 3) – 1]/4
    - S5 = [(Question 5) – 1]/6
    - S7 = [(Question 7) – 1]/6
    - S9 = [(Question 9) – 1]/4;
    - Symptom frequency score = 100*(mean of S3, S5, S7 and S9)
- Symptom burden. Symptom burden score = 100*[(mean of questions 4, 6 and 8 actually answered) – 1]/4
- Self-efficacy. Calculated as = 100*[(mean of questions 10 and 11) – 1]/4
- QoL. Calculated as 100*[(mean of questions 12, 13 and 14 actually answered) – 1]/4
- Social limitation. Calculated as 100*[(mean of questions 15a to 15d actually answered) – 1]/4
- Total symptom score = mean of the following available summary scores:
    - Symptom frequency score
    - Symptom burden score
- Clinical summary score = mean of the following available summary scores:
    - Physical limitation score
    - Total symptom score

5 Analysis data sets

Only patients for whom all core Baseline characteristics are available will be included in the final analysis; core Baseline characteristics are defined as: gender, year of birth, NT-proBNP.

For all patients fulfilling these selection criteria, the following analysis sets will be defined:

- Analysis of Baseline variables will be carried out in 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, i.e. patients who were referred to the cardiologist – the respective patient set will be labelled Follow-up Set.

6 Variables of analysis

6.1 Variables with respect to the primary objective

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 (level 1 and level 2 as described in section 4.5.1). In addition, the guideline adherence at Visit 3 will be assessed (A3).

6.2 Variables with respect to the secondary objectives

Demographics

- Age (in years)
- Age in groups (< 65, ≥ 65 to < 75, ≥ 75 to < 85, ≥ 85 years)
- Gender (Male, Female)
- Race (Caucasian, Black, Asian, Other). If "Other": Specification
- Living characteristics (Living independently in household (alone), Living independently in household (with spouse or significant other), Living in residence with family member (non-spousal or significant other), Living in a long term care facility, Transient housing)
- Environmental living situation (Urban, Suburban, Rural)
- Health insurance status (Statutory health insurance, Private health insurance, Combination of statutory and private health insurance, None)
- Highest educational level (Primary education, Secondary education, University, None)
- Employment status (Student, Employed (part time), Employed (full time), Homemaker, Retired, Unemployed, Sustained sick leave)
- General smoking status (Never, Former, Current)
- Consumption of cigarettes (Never, Former, Current).
    - If "Former" or "Current": amount of consumption in pack years.
- Consumption of electronic cigarettes (Never, Former, Current).
    - If "Former or Current": Duration of consumption (in years).
- Consumption of cigars (Never, Former, Current)
    - If "Former or Current": Duration of consumption (in years).

- Consumption of pipes (Never, Former, Current).
    - If “Former or Current”: Duration of consumption (in years).
- Consumption of chewing tobacco (Never, Former, Current).
    - If “Former or Current”: Duration of consumption (in years).
- Consumption of nicotine patches (Never, Former, Current).
    - If “Former or Current”: Duration of consumption (in years).
- Consumption of other tobacco products (Never, Former, Current).

Clinical features (Visit 1)

- Primary etiology of HF (Ischemic, Non-Ischemic).
- Primary etiology of HF if “Non-Ischemic” (Hypertensive, Diabetic, Alcoholic, Viral cardiomyopathy, Infectious cardiomyopathy, Peripartum, Drug induced, Cardiac arrhythmia, Valvular disease, Other). If “Other”: Specification
- Duration of HF (in years)
- Duration of HF in categories (> 3 years, ≤ 3 years).
- Any hospitalization due to HF in the last 12 months (Yes, No)
- Any visit of emergency room (without hospitalization) due to HF in the last 12 months (Yes, No)
- Any visit of an HF outpatient clinic or a cardiologist due to HF in the last 12 months (Yes, No)
- Performance of diagnostic procedures: Echocardiogram, Electrocardiogram, Chest X-ray, Pulmonary function test, Computed tomography of the heart, Cardiac MRI, Cardiac catheterization, Coronary angiography, 6-minute walking test, Laboratory test
- Left ventricular ejection fraction (LVEF, in %)
- Performance of therapeutic procedures: Percutaneous coronary intervention, Coronary artery bypass graft surgery, Carotid stent, Valve surgery, Cardiac resynchronisation therapy device, Cardiac resynchronisation therapy device – pacemaker, Cardiac resynchronisation therapy device – Implantable cardioverter defibrillator with pacing capabilities, Implantable cardioverter defibrillator, Left ventricular assist device, Ultrafiltration, Heart transplantation, Other. If “Other”: Specification.
- Concomitant disease:
    - Atrial fibrillation, Atrial flutter, Tachyarrhythmia, Diabetes mellitus Type 1, Diabetes mellitus Type 2, Obesity, Stable angina pectoris, Unstable angina pectoris, Asthma, Anemia, Depression, COPD, Renal disease – due to Hypertension, Renal disease – due to diabetes, Renal disease – Other, Hypertension, Carotid artery stenosis, Renal artery stenosis, Dyslipidemia, Primary hyperaldosteronism, Hyperthyreoidism, Hypothy-

reoidism, Peripheral vascular disease, Sleep apnea, Parkinson's disease, Alzheimer's disease, Peripheral neuropathy (any etiology), Dementia (other than Alzheimer's), Rheumatoid arthritis, Osteoporosis, Alcoholic liver disease, B chronic hepatitis, C chronic hepatitis, Steatohepatitis (Absent, Present)

- History of myocardial infarction, Prior stroke, Prior transient ischemic attack, History of venous thromboembolism, History of angioedema, Previous/current malignant disease (Yes, No)
- Other comorbidity (Yes, No). If Yes: Specification.

Clinical features (Visit 2 and 3)

- Concomitant disease:
  - Atrial fibrillation, Atrial flutter, Tachyarrhythmia, Diabetes mellitus Type 1, Diabetes mellitus Type 2, Obesity, Stable angina pectoris, Unstable angina pectoris, Asthma, Anemia, Depression, COPD, Renal disease – due to Hypertension, Renal disease – due to diabetes, Renal disease – Other, Hypertension, Carotid artery stenosis, Renal artery stenosis, Dyslipidemia, Primary hyperaldosteronism, Hyperthyreoidism, Hypothyreoidism, Peripheral vascular disease, Sleep apnea, Parkinson's disease, Alzheimer's disease, Peripheral neuropathy (any etiology), Dementia (other than Alzheimer's), Rheumatoid arthritis, Osteoporosis, Alcoholic liver disease, B chronic hepatitis, C chronic hepatitis, Steatohepatitis (Absent, Absent – Prior present, Present, Present – New, Present – No Change, Present - Worse)
  - Transient ischemic attack, Venous thromboembolism, Angioedema, New malignant disease (Absent, Present)
  - Previous/current malignant disease (Better, No Change, Worse)

Pharmacological treatment of HF

- ATC level 2 of HF medication at Visit 1, Visit 2 and Visit 3.
- Preferred name of HF medication at Visit 1, Visit 2 and Visit 3.
- Dose and frequency of HF medication
- Duration of HF medication at Visit 1 in groups (≤ 1 year, > 1 year to ≤ 2 years, > 2 year to ≤ 3 years, > 3 years);

NT-proBNP, stability and suitability for prospective interventional period

- NT-proBNP ever tested before Visit 1 (Yes, No)
- NT-proBNP in pg/ml at Visit 1 and Visit 3.
- NT-proBNP in groups (≥ 600 to < 800 pg/ml, ≥ 800 to < 999 pg/ml, ≥ 1000 to < 1200 pg/ml, ≥ 1200 pg/ml) at Visit 1 and Visit 3.
- Absolute Change in NT-proBNP between Visit 1 and Visit 3 (change calculated via *post minus pre value)*
- Clinical stability of the patient at Visit 1 (Yes, No)

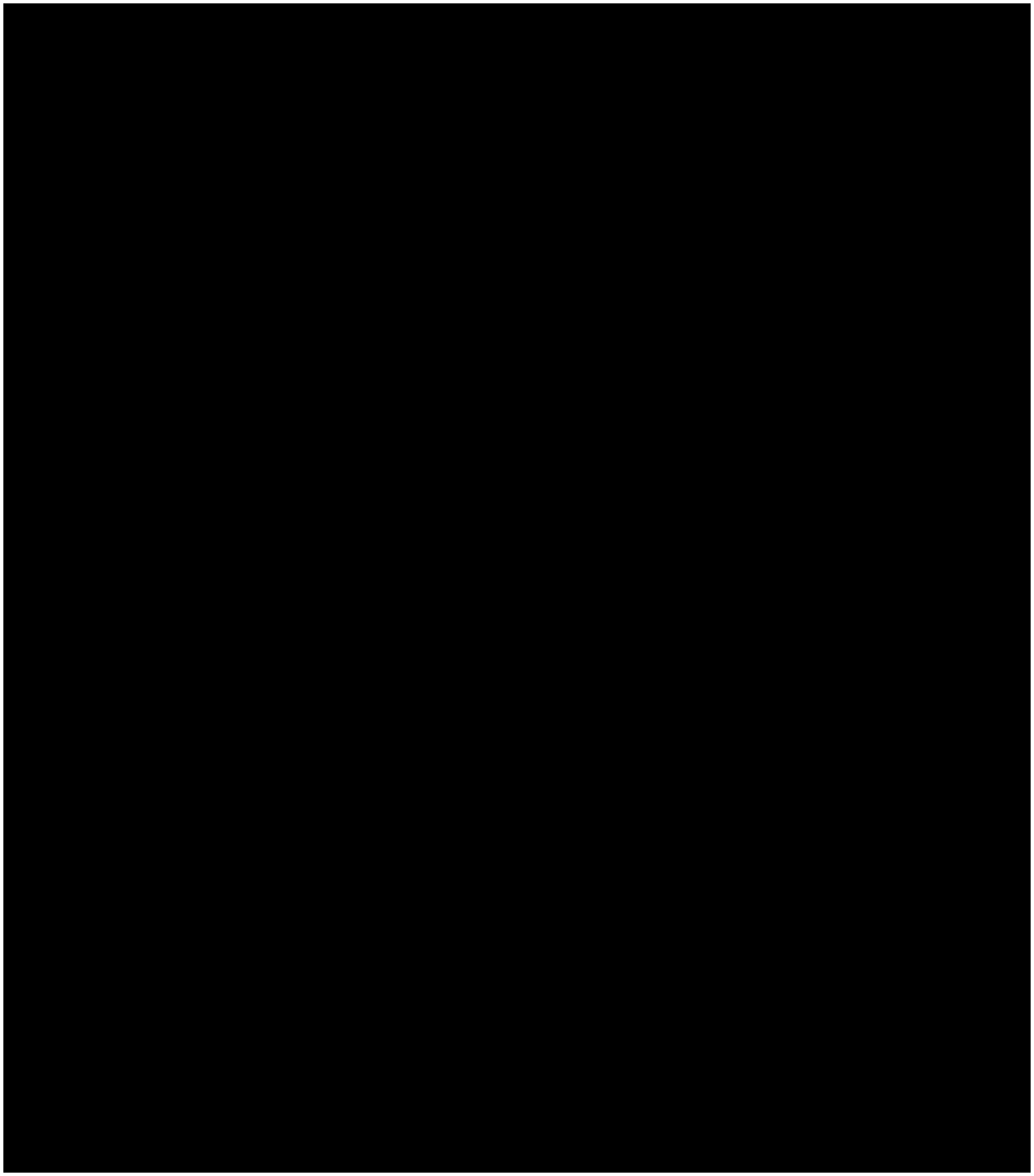
- Suitability for prospective interventional period of the study (Yes, No)
- Referral to cardiologist (Yes, No)
- Reason for non-referral to cardiologist

Cardiologist's advice

- Cardiologist's advice on therapy level (No change, Dose reduction, Dose increase, Discontinuation, New prescription)
- Cardiologist's advice on patient level (No change, Treatment intensification, Treatment reduction, Treatment adaption)
- Implementation of treatment changes by cardiologist (Yes, No, Partially)
- Acceptance of cardiologist's advice by primary care physician on therapy level (Yes, No)
- Acceptance of cardiologist's advice on patient level (All changes implemented, No changes implemented, Changes partially implemented).
- Reason for non-acceptance of the cardiologist's advice

Patient reported outcomes

- EQ-5D VAS at Visit 1, Visit 2, Visit 3, absolute change from Baseline to Visit 2 and Visit 3 and absolute change from Visit 2 to Visit 3 (change calculated via *post minus pre value*).
- EQ-5D utility index at Visit 1, Visit 2, Visit 3, absolute change from Baseline to Visit 2 and Visit 3 and absolute change from Visit 2 to Visit 3 (change calculated via *post minus pre value*).
- EQ-5D single dimensions at Visit 1, Visit 2 and Visit 3.
- KCCQ sub-scores, total symptom score and clinical summary score at Visit 1, Visit 2, Visit 3, absolute change from Baseline to Visit 2 and Visit 3 and absolute change from Visit 2 at Visit 3 (change calculated via *post minus pre value*).



6.4 Safety variables

Vital signs

- Body Mass Index (BMI), defined as *Weight (in kg)/(Height (in m))*^{2}, at Visit 1 and Visit 3
- Mean systolic blood pressure (in mmHg) at Visit 1, Visit 2 and Visit 3
- Mean diastolic blood pressure (in mmHg) at Visit 1, Visit 2 and Visit 3
- Pulse (in bpm) at Visit 1, Visit 2 and Visit 3

Signs and symptoms of HF including NYHA

- NYHA functional class (Class I to Class IV) at Visit 1, Visit 2 and Visit 3
- Existence of signs and symptoms of HF at Visit 1: Dyspnea at rest, Dyspnea upon effort, Paroxysmal nocturnal dyspnea, Fatigue, Chest pain / discomfort, Anxiety, Palpitations at rest, Palpitation on exertion, Orthopnea, Rales, Peripheral edema, Other (Absent, Present)
- Existence of signs and symptoms of HF at Visit 2 and Visit 3: Dyspnea at rest, Dyspnea upon effort, Paroxysmal nocturnal dyspnea, Fatigue, Chest pain / discomfort, Anxiety, Palpitations at rest, Palpitation on exertion, Orthopnea, Rales, Peripheral edema, Other (Absent, Worsened, Newly developed, Improved, No change)

Laboratory assessments others than NT-proBNP

- Assessment of Potassium, Haemoglobin, Serum creatinine at Visit 1, Visit 2 and Visit 3 (Normal value – not clinically significant, Abnormal value – not clinically significant, Abnormal value – clinically significant)
- Glomerular filtration rate (GFR) in ml/min according to Cockroft-Gault at Visit 1, Visit 2 and Visit 3.
- GFR in ml/min according to MDRD at Visit 1, Visit 2 and Visit 3.

Adverse events

- AE term (system organ class [SOC] and preferred term [PT])
- Serious AE (SOC and PT)
- AE related to study procedure (SOC and PT)
- Fatal AE (SOC and PT)

6.5 Other variables

General data

- Country
- Subject ID
- Study participation according to protocol (Yes, No)
- Reason for premature discontinuation
- Time between Visit 1 and Visit 2 (in days)
- Time between Visit 2 and Visit 3 (in days)

Inclusion criteria

Inclusion criteria as defined in Section 4.2.

Exclusion criteria

Exclusion criteria as defined in Section 4.2.

Protocol deviations

- Protocol deviation code

Non-HF medication

- Prior Non-HF medication (ATC level 2 and preferred name)
- Concomitant Non-HF medication (ATC level 2 and preferred name)
- Reason for Non-HF medication

7 Statistical methodology

7.1 General methodology

In general, descriptive statistical analyses will be performed. If not described differently, analyses at Baseline will be performed for all patients in the Enrolled Set and additionally stratified by inclusion into the prospective period of the study (Yes, No). Analyses regarding the prospective period of the study will be carried out in the Follow-up Set. In specific cases, analysis in the Follow-up Set will be additionally stratified by adherence to ESC guidelines before and after referral to cardiologist (ESC non-conform/ESC conform, ESC non-conform/ESC non-conform, ESC conform/ESC conform, ESC conform/ESC non-conform, details are specified below). All subgroup analyses are described below in Section 7.10.

Quantitative data (e.g. age) will be analysed by the statistical parameters valid N, missing N, mean, standard deviation, minimum (0%), median (50%), and maximum (100%).

Qualitative data (e.g. gender) will be presented by means of (absolute and relative) frequency distributions. The calculation of percentages will be based on the observed data per parameter, excluding patients with missing values (exceptions are described below). Exact Clopper-Pearson 95%-confidence intervals (CIs) will be calculated if applicable (see descriptions below).

Analyses of conditional endpoints (e.g. amount of cigarettes consumption in pack years) will be based on the number of subjects fulfilling the respective condition (e.g. patients with current or former consumption of cigarettes).

If indicated by the data, results of statistical analysis may be complemented by individual patient listings.

7.2 Disposition of patients

Analysis of patient dispositions will be performed without stratifications described in Section 7.1.

The following variables will be analysed in terms of frequency distributions describing the disposition of patients in this study:

- Number of patients in the analysis sets overall and by country (all patients)

- Protocol deviations (Enrolled Set and Follow-up Set)
- Number of patients violating inclusion and exclusion criteria (for each criterion; Enrolled Set, Follow-up Set)
- Number of patients with premature study discontinuation (Follow-up Set)
- Reasons for premature study discontinuation overall (patients with preliminary study discontinuation)

In addition, the variables at Visit 1 for *NT-proBNP, stability and suitability for prospective interventional period* (as described in Section 6.2) will be summarised without further stratification as follows:

- NT-proBNP ever tested before Visit 1 (Enrolled Set)
- NT-proBNP in groups (< 600 pg/ml, ≥ 600 pg/ml) at Visit 1 (Enrolled Set)
- Clinical stability of the patient (Enrolled Set)
- Suitability for prospective interventional period of the study (Enrolled Set)
- Referral to cardiologist (Enrolled Set – patients suitable for prospective period)

The reasons for non-referral to cardiologist will be listed by patient.

The time between Visit 1 and Visit 2 and the time between Visit 2 and Visit 3 will be summarized for the Follow-Up Set.

7.3 Description of Baseline status

The analysis of the Baseline status of the patients will be performed in the Enrolled Set (stratified by inclusion in the prospective period of the study). Summary statistics will be provided for the variables described in Section 6.2 in the sub-section *Demographics*.

The following definitions will be applied for derived variables:

- Age will be calculated as (*date of visit 1 – 1 July in year of birth)/365.25*.
- General smoking status will be classified as follows:
    - Never: “did the patient ever or does the patient currently smoke/consume tobacco” is answered with “No”
    - Current: “did the patient ever or does the patient currently smoke/consume tobacco” is answered with “Yes” **and** consumption of at least one tobacco product answered with “Current”
    - Former: “did the patient ever or does the patient currently smoke/consume tobacco” is answered with “Yes” **and** consumption of at least one tobacco product answered with “Former” **and** consumption of no tobacco product answered with “Current”
    - For patients where “did the patient ever or does the patient currently smoke/consume tobacco” is answered with “Yes” **and** consumption of all tobacco product answered with “Never” or not specified, the smoking status remains missing

- Consumption of single tobacco products: Patients where “did the patient ever or does the patient currently smoke/consume tobacco” is answered with “No” will be assigned to “Never”.
- If smoking status of cigarettes is “Former” or “Current”, the amount of consumption in pack years will be displayed. Pack years will be calculated as *estimated amount consumed on average per day (in packs) x total duration of consumption (in years)*. The number of packs per day will be estimated as *number of cigarettes per day / 20*. If the duration of consumption is not given in years, it will be transformed accordingly.
- For all other tobacco products, the duration of consumption in years will be provided for patients with consumption status “Former” or “Current”. If the duration of consumption is not given in years, it will be transformed accordingly.

For variables with category “Other”, any specifications reported will be listed.

7.4 Treatment of HF

7.4.1 HF treatment by visit

For the Enrolled Set, pharmacological treatment of HF will be analysed at Visit 1, additionally stratified by inclusion into the prospective period of the study.

For the Follow-up Set, pharmacological treatment of HF will be analysed additionally at Visit 2 and Visit 3.

HF treatment at Visit X is any treatment of HF with start date prior to Visit X or at Visit X and ongoing at Visit X.

Dose and frequency of HF medication will be concatenated for use of analysis (e.g. dose: ”10 mg”, frequency: ”OD”, combined value: “10 mg – OD”). In case, dose unit is “other”, the respective specified dose unit will be used.

The duration of specific HF medication at Visit 1 will be evaluated in groups (≤ 1 year, > 1 year to ≤ 2 years, > 2 year to ≤ 3 years, > 3 years) by preferred name; it will be derived from the calculated duration of treatment via *(date of V1 - start date)/365.25* or (in case of missing or incomplete start date) using the approximate start time of medication (1 year ago, 2 years ago, 3 years ago, > 3 years ago). In case of incomplete start date and missing approximate start time, the start date will be imputed using the methods for handling of missing values (Section 7.10). If multiple HF medications with the same code are documented for the same patient at Visit 1, the longest duration of treatment will be used for analysis.

The following analyses will be provided:

- Incidence rates for HF treatments by ATC level 2 and preferred name. For this analysis, the ATC level 2 “Diuretics” (C03) will be split up into “Diuretics – without Mineral Corticoid Antagonists” and “Diuretics – Mineral Corticoid Antagonists”. Mineral Corticoid Antagonists are any medications with ATC code C03DA.

- Incidence rates for HF treatments by preferred name and concatenated dose and frequency.
- Incidence rates for HF treatments by preferred name and duration of HF treatment (only Visit 1).

7.4.2 Adherence to ESC guidelines (primary analysis)

For each patient, HF treatment at every visit will be classified with respect to adherence to ESC guidelines on level 1 and level 2 as outlined in Section 4.5.1. Respective frequency distributions of adherence (yes, no) will be provided for the Follow-up Set for every visit.

The primary analysis will be performed on guideline adherence level 1 (as described in Section 4.5.1) as follows: based on the patients in the Follow-up Set treated not according to ESC guidelines at Visit 1, absolute and relative frequencies of A2 will be provided. The proportions within this analysis will be calculated twice, with and without considering missing values for A2. 95%-CIs will be provided for the proportions.

This analysis of A2 will be repeated for all patients in the Follow-up Set treated according to guidelines (level 1) at Visit 1.

For sensitivity, the analyses of A2 conditional to guideline adherence at Visit 1 will be repeated for guideline adherence level 2 (drug type and dose).

For the Enrolled Set, adherence to ESC guidelines (level 1 and level 2) will be analysed at Visit 1, additionally stratified by inclusion into the prospective period of the study.

In addition, the analyses of guideline adherence with respect to drug type will be repeated without taking into account the indication of the applied medications. This means, patients taking an ACEi, ARB, Beta-Blocker or MRA without HF indication will not automatically be classified as non-adherent in this analysis. Instead, these drugs will be included in the analysis and can contribute to a guideline adherent treatment of the patient.

7.4.3 Cardiologist's advice

The cardiologist's advice will be analysed within the Follow-up Set for all treatments where such an advice has been documented. The following analyses will be performed:

- Analysis on therapy level:
  - Incidence of HF treatment with an advice from the cardiologist will be displayed by preferred name and kind of advice of cardiologist
- Analyses on patient level:
  - Frequencies of cardiologist's advice on patient level will be provided, using the following categories:
    - No change: Cardiologist's advice for at least one HF treatment is "No change", no other advices are given by the cardiologist.

- Treatment intensification: Cardiologist's advice for at least one HF treatment is "Dose increase" or "New prescription" and no advice for "Dose reduction" or "Discontinuation" is given.
- Treatment reduction: Cardiologist's advice for at least one HF treatment is "Dose reduction" or "Discontinuation" and no advice for "Dose increase" or "New prescription" is given.
- Treatment adaption: Cardiologist's advice for at least one HF treatment is "Dose reduction" or "Discontinuation" and for at least on other HF treatment the advice is "Dose increase" or "New prescription".

- Implementation of treatment changes by cardiologist on patient level will be displayed, defined for all patients where the cardiologist's advice on patient level is "Treatment intensification", "Treatment reduction" or "Treatment adaption" as follows:
  - Yes: All recommended HF treatment changes of a patient are implemented by the cardiologist.
  - No: No recommended HF treatment changes of a patient are implemented by the cardiologist.
  - Partially: At least one recommended HF treatment change is implemented by the cardiologist and one other recommended HF treatment change is not implemented by the cardiologist.
- Acceptance of cardiologist's advice on patient level will be provided, defined for all patients where the cardiologist's advice on patient level is "Treatment intensification", "Treatment reduction" or "Treatment adaption" as follows:
  - All changes implemented: acceptance of all cardiologist's change advices
  - No changes implemented: non-acceptance of all cardiologist's change advices
  - Changes partially implemented: acceptance of at least one and non-acceptance of at least on cardiologist's change advice

Reasons for non-acceptance of the cardiologist's advice will be listed by patient and HF treatment.

7.5 Description of HF

Summary statistics will be provided for the variables described in the subsections *Clinical features*, [redacted] and *Diagnostic and therapeutic procedures* of Section 6.2 and Section 6.3. In detail, the following patient sets will be used for these analyses (Table 7-1):

Table 7-1 Analysis of HF

Variables from sub-section	Patient sets and stratifications used for analysis

Clinical features (Visit 1)	• Enrolled Set (all patients from Enrolled Set and additionally stratified by inclusion in prospective period of the study)
Clinical features (Visit 2 and 3)	• Follow-up Set
[redacted]	[redacted]
Diagnostic and therapeutic procedures	• Follow-up Set

The following definitions will be applied for derived variables:

- The duration of HF will be calculated as *(date of V1 - 1 July in year of first HF diagnosis)/365.25*. If this calculation leads to a negative value, the duration will be set to 1/365.25.
- In addition, the duration of HF disease will be provided in categories (> 3 years, ≤ 3 years). In case the duration of HF is missing, the approximate duration of HF reported in the eCRF will be used.

The number of hospitalizations due to HF will be provided for the patients with any hospitalization due to HF prior to the respective visit. The same algorithm will be applied for the number of emergency room visits due to HF and the number of visits in HF outpatient clinic or cardiologist.

For variables with category “Other”, any specifications reported will be listed.

7.6 NT-proBNP

NT-proBNP will be analysed at Visit 1 for the Enrolled Set, stratified by inclusion into the prospective period of the study, and at Visit 1and Visit 3 for the Follow-up Set, and additionally stratified by adherence to ESC guidelines before and after referral to cardiologist.

Summary statistics for NT-proBNP at Visit 1, Visit 3 and the absolute change from Visit 1 to Visit 3 will be provided. In case an interval is given for the NT-proBNP result, the following rules will be applied: if the value is estimated downwards (i.e. “< XX pg/ml”), the new value XX-1 pg/ml will be used for the analysis. If the value is estimated upwards (i.e. “> XX pg/ml”), the new value XX+1 pg/ml will be used for the analysis.

In addition, NT-proBNP in groups (≥ 600 to < 800 pg/ml, ≥ 800 to < 1000 pg/ml, ≥ 1000 to < 1200 pg/ml, ≥ 1200 pg/ml to <1400 pg/ml, ≥ 1400 pg/ml to < 1600 pg/ml, ≥ 1600 pg/ml to < 1800 pg/ml, ≥ 1800 pg/ml to < 2000 pg/ml, ≥ 2000 pg/ml) will be displayed by visit.

7.7 Patient reported outcomes

Patient reported outcomes as described in Section 6.2 will be analysed at Visit 1 for the Enrolled Set and at Visit 1, Visit 2 and Visit 3 for the Follow-up Set following the procedures described in Section 7.1.

7.8 Non-HF medication

Prior non-HF medication is defined as any non-HF medication with start date prior to Visit 1, concomitant non-HF medication is either any prior non-HF medication which is ongoing at Visit 1 or any non-HF medication with start date between Visit 1 (including date of Visit 1) and Visit 3 (including date of Visit 3).

Prior non-HF medication will be displayed for the Enrolled Set and the Follow-up Set, concomitant medication only for the Follow-up Set following the procedures described in Section 7.1.

Reasons for non-HF medications will be listed by patient and non-HF medication.

7.9 Safety analysis

7.9.1 Adverse events

All AEs documented in the eCRF will be analysed. Incidence rates of AEs, serious AEs, fatal AEs and AEs related to study procedures will be displayed by SOC and PT for the Follow-up set without any stratification.

In addition, a comprehensive listing of all AEs will be provided.

7.9.2 Other safety variables

Vital signs, signs and symptoms of HF including NYHA and Laboratory assessments others than NT-proBNP, as described in Section 6.4, will be analysed at Visit 1 for the Enrolled Set and at Visit 1, Visit 2 and Visit 3 for the Follow-up Set following the procedures described in Section 7.1.

7.10 Missing data and outliers

In General, no imputation of missing data will be performed for analysis of the primary variable. This means that for patients with missing LVEF at Baseline the primary variable is not evaluable. Instead, proportions based on observed data and proportions including patients with missing data will be provided (see Section 7.4.2). However, for reason of sensitivity the analyses of guideline adherence (only analyses taking into account the HF indication of treatments) will be repeated by applying the following substitution: missing LVEF values will be replaced by LVEF category “> 35%”.

Missing values in single items of patient questionnaires will be treated according to the descriptions in Section 4.5.2. Changes from Baseline cannot be calculated if either the data at Visit 1 or after Visit 1 are missing: no replacement of missing data will be performed in such cases.

Incompletely reported date variables will be imputed as follows: if day is not given, the 15th of the month will be imputed, if month is not given the 1 July of the respective year will be used for analysis. If these imputations lead to negative values when calculating durations, the respective duration will be set to one day.

Any impossible / implausible values not identified during data management processes will be treated as missing and not to be imputed

7.11 Subgroup analyses

Adherence to ESC treatment in Follow-up Set (conditional analyses of A2 on guideline adherence level 1, calculation of percentages based on observed data), the frequency of cardiologist's advice on patient level and the acceptance of cardiologist's advice on patient level will be analysed for the following subgroups:

- Gender (Male, Female)
- Age groups (< 65, ≥ 65 to < 75, ≥ 75 to < 85, ≥ 85 years)
- Duration of HF (< vs. ≥ median)
- NT-proBNP level categories at Visit 1 (≥ 600 to < 1200 pg/ml, ≥ 1200 to < 1800 pg/ml, ≥ 1800 pg/ml)
- Country clusters (Western Europe: Norway, Denmark, Belgium, France, Spain, Portugal, Italy, Malta; Eastern Europe: Russia, Hungary, Poland, Lithuania, Latvia, Estonia, Cyprus, Croatia, Slovenia, Israel)

[redacted]

In addition, all analyses (including subgroup analyses without country specific subgroup analyses) will be performed separately for patients from Belgium study centres.

7.12 Further issues

Due to the exploratory character of the study, modifications and extensions of the prespecified analyses are possible if indicated by the data. This will be documented in an analyses plan addendum.

In addition to the analysis based on the Enrolled Set and Follow-Up set, a separate analysis for patients in Belgium centres will be conducted. This analysis will be performed following the descriptions for the overall analysis in this SAP (exception: subgroup analysis by country clusters).

7.13 Deviations from the analysis planned in the study protocol

The described analyses deviate from the analyses planned in the study protocol in the following aspects:

- Analysis of HF medication will be performed by visit instead of using general classifications for "prior" and "concomitant". This enables interpretations of actual treatment status of patients without any overlay of specific treatment schemes. In addition, this analysis is consistent with the primary analysis which focusses on specific time-points.
- The results of the primary analysis were originally planned to be presented in terms of a cross table between A1 and A2. In order to increase readability and

clarity of the results, this cross table is now split up for the analysis providing the results in separate tables. The content of the primary analysis is not affected by this change.

- According to the study protocol, it was planned to perform all treatment analyses stratified by country: this was adapted to specified treatment analyses (see Section 7.11) in order to improve readability and clarity of the results.

8 References

1. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891-975.
2. Corrigendum to: '2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure'. Eur Heart J 2017.