Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure

Draft

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This guideline replaces the Note for Guidance on clinical investigation of medicinal products for the treatment of cardiac failure (CPMP/EWP/235/95, Rev 1).

Comments should be provided using this template. The completed comments form should be sent to CVSWPSecretariat@ema.europa.eu.

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chronic heart failure, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, hospitalisation, clinical trial, mortality, functional capacity, exercise testing, patient related outcomes
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Executive summary

This guideline addresses the EU regulatory position on the clinical development of new medicinal products in the treatment of patients with chronic heart failure (CHF). The aim of this document is to update the Note for guidance on clinical investigation of medicinal products for the treatment of cardiac failure (CPMP/EWP/235/95, Rev. 1). The principal changes from the previous document relate to:

(i) differentiation of types of heart failure between reduced and preserved ejection fraction;
(ii) inclusion of patients that are clinically stable early after hospitalisation for heart failure;
(iii) description of ways to measure morbidity;
(iv) assessment of efficacy criteria and the need for morbidity and mortality trials.

1. Introduction (background)

It is recognised that chronic heart failure (CHF) encompasses heterogeneous groups of patients with a wide spectrum of symptoms and different causes, resulting from an abnormality of cardiac structure or function. Within this spectrum, patients may either have heart failure with reduced ejection fraction (HFrEF) or heart failure with a moderately reduced or largely preserved ejection fraction (HFpEF) (1). The distinction between patients with HFrEF from those with HFpEF is important because they represent groups with different underlying pathophysiologic, haemodynamic and neurohormonal abnormalities, distinctly different clinical characteristics, and dissimilar efficacy of existing therapies(2).

Patients with CHF may experience reoccurring episodes of decompensation requiring hospitalisation. Reoccurring hospitalisations for heart failure (HFH) are relatively common in patients with CHF and despite their significance they are rarely used as an endpoint in clinical trials compared to "time to first HF hospitalisation"(3,4). Accounting for reoccurring events may further characterise and quantify the occurrence of morbid events throughout the follow-up period, but experience is limited and the approach gives rise to additional methodological issues.

One of the main therapeutic goals in the treatment of CHF is to improve survival. Some drug classes (ACE-inhibitors, beta-blockers, mineralocorticoid receptor antagonists, If channel blockers, vasopeptidase inhibitors) have shown to improve prognosis in patients with CHF while other classes (e.g. certain inotropes) have had a detrimental effect on survival despite a short term positive effect on intermediate endpoints. In general, mortality/morbidity data should be provided prior to approval of new therapeutic agents for the treatment of CHF. However, under certain conditions and when there is an unmet medical need, a sizeable and meaningful effect on one or more relevant clinical endpoints may lead to approval of a medicinal product provided that the cardiovascular safety profile is adequately characterised(5,6).

2. Scope

The scope of this guideline is restricted to the development of medicinal products for the treatment of patients with CHF including those in the post-acute phase of heart failure.

This guideline is intended to assist applicants during the development phase and for guidance only.

Any deviation from the guideline should be explained and discussed in the application.
3. Legal basis and relevant guidelines

This guideline has to be read in conjunction with the introduction and general principles (4) and part I and II of the Annex I to Directive 2001/83 as amended and other pertinent elements outlined in current and future EU and ICH guidelines, especially those on:

- Studies in Support of Special Populations: Geriatrics (ICH topic E7; CHMP/ICH/379/95) and related Q&A document (EMA/CHMP/ICH/604661/2009);
- Dose Response Information to Support Drug Registration (CPMP/ICH/378/95; ICHE4);
- Statistical Principles for Clinical Trials (CPMP/ICH/363/96; ICH topic E9);
- Choice of the control group in clinical trials (CPMP/ICH/364/96; ICH topic E10);
- EMA Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95 Rev. 1);
- Pharmacokinetic Studies in Man (3CC3A);
- Note for Guidance on the Investigation of Drug Interactions (CPMP/EWP/560/95);
- Guideline on clinical investigation of medicinal products for the treatment of acute heart failure (CHMP/EWP/2986/03 Rev. 1);
- Guideline on the choice of the Non-inferiority margin (EMEA/CPMP/EWP/2158/99);
- Points to Consider on Switching between Superiority and Non-inferiority (CPMP/EWP/482/99);
- Points to consider on an Application with 1) Meta-analyses 2) One pivotal study (CPMP/EWP/2330/99);
- Ethnic factors in the acceptability of foreign clinical data (ICH E5(R1)) and Reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU-population (EMEA/CHMP/EWP/692702/2008) and Q&A to ICH E5 (R1).

4. Assessment of efficacy

The main therapeutic goals in the treatment of CHF are to improve survival and to prevent deterioration of the clinical status and hospitalisations, and they should represent the primary aim of new agents developed for the treatment of CHF. Improvement in functional capacity may also be a relevant treatment goal in selected patients. The aims of treatment and assessment of endpoints are not different between patients with HFrEF and those with HFrPEF. Given that treatments effective in improving prognosis in HFrEF have not shown a similar effect in patients with HFrPEF, effects on recurrent hospitalisations and/or on functional capacity may play a larger role in the assessment of efficacy in patient with HFrPEF but experience so far is limited and this remains subject to further scientific discussion. The therapeutic effects on symptoms and quality of life are also of great importance to patients with CHF but they are more difficult to measure and have lower reproducibility. Haemodynamic changes (e.g. left ventricular ejection fraction [LVEF], left ventricular remodelling) and biomarkers are considered to provide only supportive data.
4.1. Choice of endpoints

4.1.1. Mortality

One of the main therapeutic goals in the treatment of CHF is to improve survival. Thus, mortality is to be considered as the primary endpoint either alone or as a component of a composite endpoint in combination with hospitalisation for heart failure (except under special circumstances see 4.1.3).

Although overall mortality is the preferred endpoint, cardiovascular mortality, alone or as composite endpoint, can also be considered to be the primary mortality endpoint provided that all-cause mortality is assessed as a secondary endpoint.

4.1.2. Hospitalisation for heart failure

Time to first Heart Failure Hospitalisation (HFH) can be included as part of a primary endpoint or as a secondary endpoint in clinical trials.

Endpoints accounting for recurrent HFH events may better characterise the prognosis of patients with chronic heart failure under certain conditions, in particular when cardiovascular mortality is low and/or number of eligible patients limited. However, analysis and interpretation are complicated by so-called terminal events (i.e. all-cause death, heart transplant, Left Ventricular Assisted Device (LVAD) implant) which limit the total number of HFH per subject, and these ‘terminal events’ will usually need to be addressed explicitly in the statistical analysis since certain naïve approaches to the analysis of hospitalisation rate data will not reflect the true effect of the investigational agent. Because of limited experience with such endpoints in drug development and licensing, it is strongly recommended to seek Scientific Advice, when recurrent HFH is to be used as a part of a primary endpoint (see 5.2).

In addition, patients are often managed for episodes of transient decompensation or worsening heart failure (WHF) in outpatient settings (e.g. emergency departments, observation units, other outpatient settings)(7). The capture of events of WHF without hospitalisation may be warranted as an additional endpoint.

4.1.3. Functional capacity

Exercise testing allows objective evaluation of functional capacity in patients with CHF and may be relevant to measure as secondary endpoint under certain conditions, e.g. patients with HfPEF.(8) In selected patient populations with an unmet medical need (e.g. patients with cachexia or frail or elderly) the effect of the treatment on exercise capacity may be considered as a primary endpoint provided it is accompanied by an improvement in patient related outcome and that the cardiovascular safety profile is adequately characterised (see also 7.5 and 8.1). Further confirmation with morbidity and mortality data after registration may be required. Also, the clinical relevance of the change in exercise capacity with the treatment needs to be defined clearly.

4.1.4. Patient reported outcomes

Patient reported outcomes (PROs) may include improvement of symptoms (NYHA classification) and quality of life (QoL). Improvement of symptoms must be clinically important in magnitude, consistently achievable and sustained over an extended duration of treatment.

PROs can be used as secondary endpoints in CHF studies and should be considered as supportive. In patients with advanced disease and/or severe co-morbidities (end stage CHF, CHF with cachexia)
where there is a need for palliative care, PRO may be relevant in support of the effect on exercise capacity.

4.1.5. Haemodynamic parameters

Although worsening in some haemodynamic parameters (left ventricular function, cardiac index) are associated with poor prognosis the correlation between improvement of haemodynamic parameters with prognosis and/or symptoms has not been adequately established. Changes in haemodynamic parameters may be useful to elucidate the mode of action and the required dose of a therapeutic agent in early phase studies but cannot be used as primary endpoint in a pivotal trial.

4.1.6. Biomarkers

Although several biomarkers (neuroendocrine, renal, and cardiac) have been shown to be independent predictors of outcome in patients with CHF, none has been shown to be a reliable surrogate for clinical outcomes in patients with HF. To this end biomarkers cannot be included as primary endpoints in phase III clinical trials in CHF. Biomarkers, in particular BNP, NT-proBNP, MR-proANP or pro-enkephalin, procalcitonin may be used to better identify patients with CHF and subsets of patients likely to benefit from specific interventions.

4.1.7. Events from implantable devices

Implantable cardioverter devices (ICDs) improve survival in patients with CHF and may be used to record episodes of life-threatening arrhythmia/ventricular fibrillation (see also 8.4). If the ventricular fibrillation or ventricular tachycardia leads to a discharge/therapy from the device, the event may be used as a measure of efficacy. Such device interventions could include shocks or anti-tachycardia pacing to overcome sustained VT. It will be necessary to distinguish improper or inappropriate shocks from successful therapies.

4.1.8. Composite endpoints

Composite and hierarchically-ordered endpoints can be applied to CHF studies providing that mortality (overall or cardiovascular) and HFH are the first two hierarchical endpoints, respectively. These endpoints may be followed in order of relevance by measures of functional status (6 Minute Walking Test [6MWT], Maximum Oxygen Uptake [MVO2]), and PRO. Please refer to the Concept paper on the need for a guideline on multiplicity issues in clinical trials - draft (EMA/286914/2012).

5. Methods to assess efficacy

Efficacy variables may be influenced by changes in concomitant background medications. Therefore, if possible, every effort should be made during the conduct of a study in patients with CHF to maintain stable background therapy throughout the study. The influences of background treatment modifications on efficacy endpoints should be carefully considered and critically scrutinised.

5.1. Survival

Efforts should be made to define the specific mode of cardiac death occurring in the studies (e.g. sudden cardiac death, pump failure, acute coronary events). It is mandatory to report and centrally adjudicate all mortality data in all studies in CHF where survival is an endpoint of the study.
Assessment of cardiovascular mortality will commonly result in ‘censoring’ of other “types” of mortality in the analysis(9). A comprehensive interpretation must address the plausibility of an assumption that this censoring is uninformative and discuss results alongside analyses including all-cause mortality. Data should be gathered so as to enable evaluation of the clinical causes of reduction in mortality (such as arrhythmias, stroke, myocardial infarction, non-cardiovascular, etc.).

5.2. **Hospitalisation for heart failure (HFH)**

Since patients with CHF may be often hospitalized for non-cardiac causes or for reasons unrelated to worsening of CHF, objective evidence of cardiac de-compensation as cause of hospitalisation should be provided. HFH must be defined in the protocol by signs and symptoms of deteriorating clinical conditions along with increased plasma levels of natriuretic peptides as appropriate and the need for acute treatments for CHF (e.g., increase in diuretic dose, intravenous diuretics, or intravenous vasodilators/inotropes).

HFH needs to be centrally adjudicated. Also, hospitalisation for cardiovascular causes but not primarily due to CHF must be noted and adjudicated. Efforts must be put in place to differentiate hospitalisations due to heart failure from those due to extra-cardiovascular causes (e.g. COPD).

Other cardiovascular events (e.g. new myocardial infarction or stroke) may be responsible for therapeutic interventions in patients with CHF. Therefore, the reasons for a change in the background therapy should always be carefully recorded and the criteria for these events must be pre-specified in the protocol. A blinded review by an independent adjudicating committee is recommended.

As described in 4.1.2, quantifying recurrent HFH events may better characterise the effect of treatment in some circumstances, but experience with this type of endpoint is limited(4). An applicant may seek Scientific Advice should include a discussion on the ways in which recurrent hospitalisations may be characterised and aspects of trial planning in respect of sample size, duration of follow-up and effect size(s) (considering the effect of treatment on HFH rate and the rate of terminal events) that can be regarded as being of clinical importance, in addition to the approach to statistical analysis.

Patients should be followed for events of interest regardless of adherence to randomized treatment, with all events included in the primary analysis unless otherwise justified.

Further, the threshold for hospitalisation is highly variable across (and within) regions of the world which may affect the interpretability and applicability of study results to the European population. This should be taken into account when planning the studies, e.g. by implementation of similar criteria for hospitalisation and stratification by regions.

Patients should be followed for events of interest regardless of adherence to randomized treatment, with all events included in the primary analysis unless otherwise justified.

In order to define an episode of de-compensation in the outpatient settings it is required to demonstrate a cardiac cause for the worsening of symptoms using the same definitions as for HFH.

5.3. **Functional status**

Measurements of maximal oxygen consumption during bicycle or treadmill exercise (MVO2) and of supervised 6MWT are both reliable methods for the assessment of functional capacity. Other functional tests, such as stair climb test, Short Physical Performance Battery (SPPB) or hand-grip strength assessment, may be more appropriate in selected populations (elderly, frail, cachexia, etc.).
Exercise testing should be performed using appropriate protocols specifically designed for the functional assessment of patients with CHF (5). Sub-maximal exercise protocols should specify a priori the reasons for termination of the tests. Patients naive to exercise protocols (bicycle, treadmill, measurement of oxygen consumption) should first be made familiar with the technique before they are included in the trial. Repeated baseline and repeated follow-up testing may reduce variability of the results and increase statistical power.

5.4. Haemodynamic studies and studies of left ventricular function

A variety of techniques are available for both non-invasive and invasive measurements of cardiovascular haemodynamics and left ventricular function that may include ventricular dimensions, ejection fraction and indices of systolic and diastolic functions (e.g. Left ventricular end diastolic pressure [LVEDP]).

The use of newer techniques used to study the haemodynamic effect of a new agent in CHF must be validated beforehand and justified. Non-invasive techniques including echocardiography, Doppler studies, radio-isotope ventriculography and cardiac magnetic resonance imaging have been proven to be objective and quantifiable. Some of these techniques show inter-operator variability. Measurement of LVEF by an isotopic method and/or by cardiac magnetic resonance imaging and/or echocardiography is desirable to quantify the degree of systolic ventricular dysfunction and its response to treatment. They are also useful in defining patient subgroups (e.g. HFrEF versus HfPEF). Given the inter-operator variability, the investigators from each centre should specify the norms for their laboratory and the inter as well as intra-operator variability. Variability can be reduced by core laboratory analyses.

5.5. Patient reported outcomes

5.5.1. Clinical Symptoms

Several symptoms scores or global or disease-specific assessments can be used to assess the effect of a new pharmacological agent on clinical symptoms. The most commonly used classification system for the assessment of symptoms in patients with CHF is the New York Heart Association (NYHA) classification. Other scales or scores can be used for the assessment of symptoms provided that they are validated in the populations (and in the languages) in which they are being tested. Whatever scale is used, it must be capable of providing robust evidence of symptomatic improvement. However, NYHA class as an established standard should be documented to allow comparisons across trials.

5.5.2. Quality of Life (QoL)

Several QoL questionnaires can be used for the assessment of the treatment effect in patients with CHF. Questionnaires must be fully validated for the disease. In order to be considered, questionnaires must be translated and validated in all the languages spoken in the countries of patients included in the clinical studies.

6. Selection of patients

6.1. Study population

Patients with CHF can be defined as those with an abnormality of cardiac structure or function leading to failure of the heart to deliver blood at a rate commensurate with the metabolic requirements. Patients to be included in clinical trials will have to be diagnosed with CHF according to the current ESC/HFA Guidelines for the diagnosis and treatment of acute and chronic heart failure (1).
should be given to the representativeness of the study population, patients included in the trials must
represent the real life population. A relevant number of patients over 75 years of age must be
included.

Patients with CHF must differentiated according to the degree of left ventricular function (LVEF)
between those with reduced (LVEF <40%) and those with preserved ejection fraction (LVEF >40%)
(HFrEF and HfPEF respectively). Patients with HfPEF may be further differentiated between those with
a moderately reduced (LVEF 40-50%) or largely preserved ejection fraction (LVEF >50%)(1). EF
should be defined before inclusion in the study. Studies can be conducted in a large population
encompassing all types of heart failure or they can be limited to one or two subgroups.

Patients hospitalised because of an acute episode of de-compensation who are stabilized by standard
therapy and are not receiving parenteral treatments but remain hospitalised are defined as patients
hospitalised for heart failure (HFH); these patients can be included in studies to assess the effect of
chronic therapies that are started during the hospitalisation, at discharge or during the 30 days after
hospital discharge.

The pathophysiology of CHF studied should be defined in terms of aetiology as much as possible (i.e.
ischaemic, hypertensive, iatrogenic, diabetic etc.). Patients entering phase IIb and III clinical trials
with agents for the treatment of heart failure (NYHA class II-IV) should be treated at study entry as
per clinical practice guidelines (1). Given the worldwide variability in therapeutic practices a sizeable
number of patients included in clinical trials should be representative for the European population with
regards to their background treatment and standard of care.

In some trials it may be necessary to “enrich” the number of events by further restriction of LVEF or
other patient characteristics. This should be discussed further within the context of the external validity
for the claimed indication. This also applies to selection on the basis of pre-treatment and tolerance of
the drug.

7. Study design

For studies to be conducted in patients with CHF, a period of stability of CHF medications is required
before inclusion. In patients with CHF, uptitration of first line therapies should be conducted according
to current clinical practice guidelines (1).

7.1. Pharmacodynamics

Pharmacodynamic (PD) studies should include, apart from the evaluation of tolerability, the
assessment of duration of action, the effect of the agent on haemodynamic parameters (e.g. stroke
volume, Pulmonary Capillary Wedge Pressure [PCWP]), heart rate, as well as the effect on impulse
formation, conduction and repolarisation (i.e., QT/QTc intervals) and cardiac arrhythmia, neuro-
hormonal parameters (e.g. sympathetic nervous system) and renal function.

Patients with degrees of CHF ranging from mild to severe need to be studied, depending on the
indication claimed. The PD activity of the substance needs to be defined with regard to cardiac
contractility, arterial and venous tone, and diastolic/systolic function of the heart. If an effect on
cardiac electrophysiology of the investigational agent is proposed for or if it is involved in the beneficial
effects of the agent, a potential for pro-arrhythmic effect should be fully explored. Further studies -
depending on the mechanism of action of the product - may include assessment of myocardial oxygen
consumption, and coronary and regional blood flow.
7.2. **Pharmacokinetics**

The pharmacokinetic (PK) information required for a new pharmacological agent is stated in detail in the appropriate *Guideline on Pharmacokinetic Studies in Man* (3CC3A, page 99-106, Oct 1988). The pharmacological activity of the main metabolites should be quantified and studied in detail if they are likely to contribute substantially to the therapeutic or toxic effects. However, it must be taken into account that in patients with CHF drug absorption, distribution, metabolism and excretion as well as its delivery to various tissues may be altered. Therefore, depending on PK additional data should be provided.

7.3. **Interactions**

Special attention should be devoted to potentially useful or unwanted PK and PD interactions with other drugs that might be used alongside the investigational drug for combined treatment of CHF and its most common co-morbidities.

7.4. **Exploratory therapeutic studies**

The objectives of these studies will be to determine the appropriate therapeutic range including dose-concentration-response relationship of the new investigational agent and to identify patients who may benefit from the medicinal product. Before starting a pivotal trial, the optimal/appropriate clinical dose(s) to be used must be identified by adequately powered carefully designed dose-response study(ies). Dose ranging studies in CHF should thoroughly assess the lower end of the effective dose range. A parallel, fixed dose, double blind placebo controlled design has proved useful in evaluating new drugs. Dose-response studies should be randomised, placebo-controlled and double-blinded often using at least 3 dosages with a total therapy phase of at least 12 weeks to establish the clinically useful dose-range as well as the optimal dose. The dose schedule selected for pivotal studies must be justified on the basis of the results of the dose-finding studies in the target population. The endpoints in dose-ranging studies should be tailored according to the medicinal product in question and such studies should assess clinical symptoms as well as well validated non-invasive haemodynamic responses. If an appropriate dose schedule cannot be established in these initial studies, it may become necessary to investigate more than one dose in the main therapeutic studies. Based on the information from dose-concentration and concentration-response relationships, dose schedules should be clearly defined for patients with varying degrees of congestive heart failure, renal dysfunction and/or hepatic dysfunction.

7.5. **Confirmatory therapeutic studies**

Controlled double blind randomised studies are required. One large well controlled trial of adequate statistical power may be sufficient to confirm the efficacy of a new drug - provided it is soundly based and well designed, executed, reported and the results are unequivocal. A control group on placebo is preferable if ethical considerations permit, in particular when it is proposed to indicate the investigational drug as an add-on to an existing therapy. Confirmatory studies using an active control may also be acceptable depending on its place in therapy and the benefit established with the reference therapy. These should be designed to demonstrate the non-inferiority or superiority of the new agent to an active comparator. Every effort should be made to record deaths that occur after the withdrawal of double-blind treatment.
Groups should be sufficiently balanced in respect of age, sex, pathology, co-morbidities, state of disease, severity of disease and duration of symptoms. Stratified allocation may sometimes be desirable. Concomitant background treatment should be kept as similar as possible during the study. Background therapy should be given according to current guidelines.

At least one controlled study of a minimum duration of 6 months is mandatory to demonstrate efficacy in relation to functional benefit when this is the primary endpoint. In this case sufficient data to characterise the cardiovascular safety profile will be needed before approval (see also section 4.1.3.).

7.6. Studies in special populations

The efficacy studies should include patients reflecting the real life population of patients with CHF. Generally these will mainly include patients with mild to severe CHF. Subgroup analyses for gender, race, age, etc. are desirable in order to demonstrate consistency across groups. Studies in specific subgroups may be conducted. Adequate representation of elderly patients should be ensured.

Given the frequent drug-drug interactions and the need of dose re-adjustments in patients with heart failure and important co-morbidities (diabetes mellitus, COPD, renal failure, cachexia and/or sarcopenia, anaemia) additional data may be obtained in these patients. Specific studies are needed when specific information is to be included. Dose schedules should be clearly defined for elderly patients and those with various risk factors.

8. Safety aspects

As treatment of CHF is usually prolonged, long-term data on adverse effects should be provided.

All adverse effects occurring during the course of clinical trials should be fully documented. Any groups especially at-risk should be identified. Special efforts should be made to assess potential adverse effects that are characteristics of the class of drug being investigated. Particular attention should be paid to the following specific side effects:

8.1. Cardiovascular safety

If the basis for an approval is morbidity data, mortality data are expected to be available in the database in order to ensure that the cardiovascular safety profile is adequately characterized. Such data could arise either from several trials or alternatively within the pivotal study by the use of all-cause mortality with a well defined and acceptable non-inferiority margin. Interim analyses of pooled trial data can be acceptable to rule out an excess risk at initial submission. In case of interim analyses of pooled data maintenance of investigator blindness should be maintained until completion of the study. Please refer to the Reflection paper on assessment of cardiovascular risk of medicinal products for the treatment of cardiovascular and metabolic diseases (EMA/50549/2015) for further clarifications with respect to data needed for the evaluation and quantification of the cardiovascular safety profile at time of licensing.

8.2. Hypotension/bradycardia

These may be either symptomatic or asymptomatic. Special attention should be paid to first-dose phenomenon, hypotension and bradycardia following an increase in dose.
8.3. **End-organ consequences (kidney, heart, CNS)**

Effect of alterations in regional blood flow in other organ systems, especially the kidney, heart and brain, may be studied. Special emphasis should be put on renal function and electrolyte homeostasis.

8.4. **Effect on cardiac rhythm**

It is essential to investigate the potential for pro-arrhythmic effects. These investigations should include electrocardiography and continuous ambulatory monitoring which may require to be supplemented by some electrophysiological studies. In patients with implanted devices events recorded by the device are acceptable.

8.5. **Pro-ischaemic effects**

Drugs used in the treatment of CHF may increase myocardial oxygen consumption. Together with potential hypotensive effects, this may lead to angina pectoris and myocardial infarction. Therefore, the safety data should include details which characterise the potential pro-ischaemic effects of the drug.

**Definitions**

- 6MWT = 6 Minute Walking Test
- CHF = Chronic Heart Failure
- COPD = Chronic Obstructive Pulmonary Disease
- CNS = Central Nervous System
- ESC = European Society of Cardiology
- EU = European Union
- FDC = Fixed Dose Combination
- HFA = Heart Failure Association
- HFH = Heart Failure Hospitalisation
- HFrEF = Heart Failure with reduced Ejection Fraction
- HfPef = Heart Failure with preserved Ejection Fraction
- LA = Left Atrium
- LV = Left Ventricle
- LVAD = Left Ventricular Assisted Device
- LVEDP = Left ventricular end diastolic pressure
- LVEF = Left Ventricular Ejection Fraction
- MVO2 = Maximum Oxygen Uptake acronym for Cardiopulmonary Exercise Test
- NYHA = New York Heart Association
- PCWP = Pulmonary Capillary Wedge Pressure
PROBE= Prospective Randomized Open Blinded Endpoint
PROs= Patient Related Outcomes
QoL= quality of life
VF= Ventricular Fibrillation
VT= Ventricular Tachycardia

References
1. ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2016: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2016 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. In preparation.