EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 February 2013
EMA/CHMP/87576/2013
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for revision of note for guidance on clinical investigation of medicinal products for the treatment of cardiac failure (CPMP/EWP/235/95)

Draft

Agreed by Cardiovascular Working Party	30 January 2013
Adopted by CHMP for release for consultation	11 February 2013
Start of public consultation	01 March 2013
End of consultation (deadline for comments)	31 May 2013

The proposed guideline will replace The Note for Guidance on clinical investigation of medicinal products for the treatment of cardiac failure (CPMP/EWP/235/95).

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

Keywords	*Heart Failure, left ventricular function, mortality, morbidity, hospitalisation*

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1. Introduction

Chronic Heart Failure (CHF) encompasses heterogeneous groups of patients with a wide spectrum of symptoms and different causes. The *CHMP Guideline on the clinical investigations of medicinal products for the treatment of cardiac failure (CPMP/EWP/235/95)* addresses the development issues in this specific patient population. Recently, it became apparent that the scope of the guideline should be widened to include patients who are encountered in clinical practice and not previously addressed, including patients with preserved ejection fraction and with heart failure stabilised after an acute event, and also to elaborate on the endpoints to be studied.

2. Problem statement

Heart failure is a syndrome with a wide spectrum ranging from asymptomatic left ventricular dysfunction to end-stage heart failure. Within this spectrum, patients may either have heart failure with reduced ejection fraction (HFrEF) or heart failure with a normal or relatively preserved ejection fraction (HFpEF). They may also oscillate between periods of stability, where they are generally well managed as outpatients (i.e. chronic heart failure), and periods of de-compensation requiring hospitalization [i.e. hospitalized heart failure or acute heart failure syndromes (AHFS)].

Amongst patients with heart failure it is important to differentiate those with HFrEF from those with HFpEF. This distinction is important because these represent groups with different underlying patho-physiological, haemodynamic, and neurohormonal abnormalities and distinctly different clinical characteristics, varying risks for adverse outcomes, and dissimilar efficacy of existing therapies.

Standard therapies for patients who are stable after an acute episode of de-compensation do not curb the high mortality and re-hospitalization rates over the weeks to months following hospital discharge. While mortality for patients with HFrEF has decreased and remains relatively low, for patients hospitalised for HF mortality at 60-90 days is approximately 15% and reaches 30% at 1 year despite existing therapies.

At present, patients hospitalised because of an acute episode of de-compensation who are stabilized by standard therapy cannot be included in trials designed for patients with acute heart failure (AHF) – because of the relatively long time elapsed since hospital admission - nor in studies designed for patients with CHF – because they are not considered stable. For the same reason patients who are in the early phases after hospital discharge cannot be included in studies designed for patients with CHF. Therefore, there is a need to identify a new category of patients with heart failure that will allow the inclusion in heart failure trials of patients that at present cannot be included in either acute or chronic heart failure studies and that are at high risk of future rehospitalisation and events.

Hospitalization for heart failure (HHF) is frequently included as a co-primary endpoint or as part of a composite primary endpoint in heart failure trials. Despite the clinical relevance of HHF, its use as an endpoint in heart failure trials is controversial since the decision to hospitalize and the threshold for hospitalization are variable across regions of the world and may affect the interpretability and

applicability of study results in specific regions, particularly in global trials. Local standards of care (such as length of stay or availability of out-of-hospital treatment resources) may differ substantially in a clinical trial. Although there is a relatively robust consensus on using heart failure hospitalization as an endpoint in heart failure trials, there is a need to better define HHF and to harmonise the definitions for related endpoints.

Furthermore, recurrent hospitalizations are a common occurrence in patients with heart failure, and they impose a substantial clinical and economic burden on patients, caregivers, physicians, and health systems. Despite their importance, repeat events are ignored in the majority of clinical trials in favour of "time to first event" analysis. Accounting for repeat events may both achieve practical gains (e.g. increased statistical power with smaller sample sizes due to higher number of events) and better characterize and quantify the patient's journey throughout the follow-up period.

Endpoints that may reflect manifestations of disease patho-physiology (e.g. biomarkers or parameters for remodeling), are often applied in earlier phases of drug development. However, available biomarkers and changes in left ventricular remodeling have not been shown to be able to predict the clinical efficacy of drug therapies in further clinical trials in heart failure. Therefore, their role in the early phases of drug development should be revised.

3. Discussion (on the problem statement)

It is proposed that there should be discussion regarding the need to update the *CHMP Note for Guideline on the clinical investigations of medicinal products for the treatment of cardiac failure (CPMP/EWP/235/95)* in order to further enhance the following aspects:

1. The inclusion of patients who are stable early after an acute de-compensation.
2. The definition of Heart Failure according to the presence or absence of left ventricular dysfunction.
3. Ways to measure the endpoint of hospitalisations.
4. The definition of endpoints that may be useful in the earlier phases of drug development in heart failure for further clinical trials.

4. Recommendation

The EMA Cardiovascular Working Party (CVS WP) recommends revising the *CHMP Note of Guidance on clinical investigation of medicinal products for the treatment of cardiac failure*. Given the relevance of the note of guidance it is advisable that, in order to prepare a scientifically sound proposal that may adequately address the major problems identified, to exchange views with experts in the field, such as the expert group on heart failure of the relevant healthcare professionals organisations (i.e. Heart Failure Association of the European Society of Cardiology [HFA of the ESC]).

5. Proposed timetable

A period of 3 months to arrange appropriate expert consultation will be needed. A draft document may be released 3 months after adoption of the Concept Paper. This will then be released for 6 months of

external consultation and following the receipt of comments it will be finalised within approximately 3 months.

6. Resource requirements for preparation

It is not anticipated that expert consultation will require convening any specific formal meeting at the EMA premises. The preparation will involve the CVS WP at the EMA. One rapporteur from the CVS WP will be involved in drafting of the document that is to be discussed during 2 CVS WP meetings. Involvement of the SWP may be required.

7. Impact assessment (anticipated)

The document is intended to provide guidance to industry when performing trials to develop drugs in patients with either CHF or heart failure stabilised after an acute event. It should also provide a clear basis for the CHMP when assessing data from studies for heart failure drugs and providing advice in this field.

8. Interested parties

Heart Failure Association of the European Society of Cardiology.

9. References to literature, guidelines, etc.

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