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

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

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Executive summary

The CHMP Guidance on the Clinical Investigation of Medicinal Products for the Treatment of Cardiac Failure (CPMP/EWP/235/95, rev. 1) provided limited regulatory guidance for development of medicinal products for the treatment of acute heart failure (AHF). This led to the development by the CHMP of the Addendum on clinical investigation of medicinal products for the treatment of acute heart failure (CPMP/EWP/2986/03).

The current document is a revised version of this Addendum and the text has been updated in relation to certain factors. In particular, patient characteristics that impact on outcome of AHF trials and their evaluation such as, need for standardisation of time of enrolment in clinical trials, time-points to assess symptoms, use of the composite endpoints, value of invasive haemodynamic measurements and role of natriuretic peptides are addressed.

1. Introduction (background)

Acute Heart Failure represents a very heterogeneous group of patients with certain common features, characterised by a rapid onset of a wide spectrum of symptoms and signs, accompanied by haemodynamic abnormalities and neuroendocrine activation secondary to abnormal cardiac function. Operationally, AHF may be defined as heart failure with signs and symptoms leading to an unplanned hospital admission. The term AHF in this document refers to acute left ventricular or concomitant right and left ventricular failure with or without pre-existing cardiac disease. AHF is often used interchangeably with the term acute heart failure syndromes (AHFS).

Acute exacerbation of chronic heart failure (CHF) previously controlled with therapy often termed “acute decompensated heart failure (ADHF)” [1] is the most common clinical entity. Causes of AHF include acute coronary syndrome (ACS), valvular heart disease and severe hypertension. Acute onset atrial fibrillation or other atrial arrhythmias are important factors in precipitating AHF. AHF may be related to systolic or diastolic dysfunction or to a mismatch between preload and afterload, and occur in the peri-operative setting of cardiac or non-cardiac surgery. Isolated acute right ventricular heart failure often differs from other forms of AHF as regards to aetiology and management and is not specifically covered in this guideline.

The clinical presentations include pulmonary oedema, cardiogenic shock or ADHF that may present with signs of systemic or pulmonary congestion, peripheral oedema or a combination. Perioperative AHF is a distinct entity as the symptoms cannot be assessed and other clinical parameters will dominate. The differing pathophysiology is likely to influence the management strategy and the clinical trials needed to investigate interventions or treatments. There are however, aspects to the treatment of AHF which are common in all forms aimed at achieving rapid relief and improvement of symptoms, stabilisation of the clinical status, correction of the underlying cause, minimisation in hospital complications, reduction in hospital readmissions and mortality. The relative order, importance and application of particular interventions are determined by aetiology and clinical presentation which in turn impact the design of the studies used to evaluate drugs for AHF (or AHFS) including patient selection and criteria for inclusion.

There is recent recognition of a group of Hospitalised for Heart Failure (HFH) patients who are often excluded from AHF or CHF trials. This group includes those with CHF that do not fulfil the definition of AHF but are hospitalised and patients that remain in hospital with partial recovery following management of an episode of ADHF. Re-hospitalization and event rates in such a group are still considerable, varying between 10-15% per year. There is a need to define such HFH patients

adequately in order to allow their inclusion in heart failure trials (see also *Note for Guidance on clinical investigation of medicinal products for the treatment of cardiac failure (CPMP/EWP/235/95, Rev 1)*).

The current interventions used for AHF include pharmacological treatments, non-pharmacological interventions (e.g. respiratory support or ventricular assist devices) and surgery (such as valve repair or replacement and heart transplant).

2. Scope

This document aims to provide guidance to applicants on the main regulatory requirements that are expected in the development of a medicinal product for treatment of AHF in adults. The main focus of the document will be pharmacological intervention of left ventricular dysfunction with or without concomitant right ventricular dysfunction. Other trials and interventions, including pacing modalities or other devices to provide mechanical support, are not within the scope of this document.

3. Legal basis and relevant guidelines

This guideline has to be read in conjunction with the introduction and general principles and parts I and II of the Annex I to Directive 2001/83/EC as amended. Pertinent elements outlined in current and future EU and ICH guidelines, should also be taken into account, especially those listed below:

- General Considerations for Clinical Trials (ICH E8);
- Dose-Response Information to support Drug Registration (CPMP/ICH/378/95; ICH E4);
- Statistical Principles for Clinical Trials (CPMP/ICH/363/96; ICH-E9);
- Choice of Control Group and Related Issues in Clinical Trials (CPMP/ICH/364/96; ICH E10);
- Points to Consider on Switching between Superiority and Non-inferiority (CPMP/EWP/482/99);
- Points to consider on multiplicity issues in clinical trials (CPMP/EWP/908/99) and draft concept paper (EMA/286914/2012);
- Note for Guidance on the Investigation of Drug Interactions (CPMP/EWP/560/95);
- Studies in Support of Special Populations: Geriatrics (ICH E7 CPMP/ICH/379/95) and related Q&A document (EMA/CHMP/ICH/604661/2009);
- CHMP Note for Guidance on the Clinical Investigation of Medicinal Products for the Treatment of Cardiac Failure (CPMP/EWP/235/95, rev. 1);
- 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 (EMA/CHMP/EWP/692702/2008) and Q&A to ICH E5 (R1).

4. Evaluation of efficacy

Therapeutic measures utilised in AHF aim to relieve symptoms and/or reduce mortality and morbidity. The expected effect of treatment will depend on the pharmacological profile or the mechanism of action of the drug, the aetiology of heart failure and the constellation of symptoms or signs at presentation. The mechanisms of action may be to improve haemodynamics, cardiac contractility,

reduce fluid overload, or to limit unfavourable neuroendocrine activation and, these will determine the endpoints including the timing of measurement. Based on data from recently completed trials, several clinical features such as systolic blood pressure (SBP) at admission or renal function and the underlying aetiology significantly influence not only efficacy but also the overall outcome of the trial. Even in ADHF (where shock is not common), admission SBP is noted to influence the overall benefit-risk balance (and prognosis). Similarly, admission renal function and its progression through the hospital admission to post discharge period may influence the overall outcome.

In AHF/ AHFS, it is expected that improvement will be demonstrated in either short term or longer term measures. Short term measures (hours to days) would mainly rely on consistent improvement in symptoms including dyspnoea and improved signs of congestion. The main measure of efficacy would be mortality (in hospital or at 30 days) as it remains high in patients with AHF. Supportive efficacy information as secondary measures might include readmissions to hospital for heart failure, days of hospital-free survival (days alive and out of hospital) and, reduction in biomarkers such as NT-pro BNP but their value as surrogates is unproven.

Different measures of efficacy might be applicable depending on the aetiology of AHF. It is important that the events and measures of efficacy should be classified as heart failure related and non-heart failure related. For example, in AHF following ischemic events (unstable angina, or acute MI), reduction in ischemia related events are likely to be the crucial measures. The timing of evaluation of efficacy should reflect the anticipated duration of treatment. When longer term administration of the agent (weeks or months) is proposed or intended, the timing of the primary endpoint should be chosen appropriately to support the duration of treatment.

With globalisation of clinical trials, there is the need to address the issue of consistency and uniformity in characteristics of patients recruited into the trials. Variations may exist in clinical practice, clinical guidelines or local treatment preferences, and these might influence the overall estimate of treatment effect and indeed the result [2]. This variability also includes reasons for hospitalisation. Efforts should be made within the development programmes to limit excess heterogeneity. Baseline characteristics and concomitant treatments should be standardised as far as possible within the context of the representativeness of the trial population. Stratification or use of appropriate statistical methods that address heterogeneities might be used with adequate justification and reasoning.

For AHF trials often there is a question about the best comparator to be deployed. Placebo might be appropriate provided the best standard of care is used in an add-on situation. Where there is an approved agent for treatment of AHF, this would be expected as the comparator (see also section 6.3).

4.1. Primary endpoints

It is well recognised that outcomes in AHF (or AHFS) are influenced by advances in treatments for chronic left ventricular dysfunction and improved survival of certain subsets of patients. However, the mortality in AHF still remains reasonably high and this will influence the choice of the primary endpoint in clinical trials. The choice of the endpoints will also depend on the pharmacological profile and mechanism of action of the medicinal product.

4.1.1. Mortality

The preferred primary endpoint is mortality (CV mortality or all-cause mortality), especially at 30 or 60 days, as the treatment for AHF is often short term administration (≤ 7 days) of the investigational agent. Additional analysis of in-hospital mortality will be of interest and relevance. Efforts should be made to present this information.

Longer term outcomes such as 6 months or 1 year all-cause mortality are also relevant and could be used as primary endpoints depending on the pharmacological profile of the medicinal product, the duration of administration and the patient population. For medicinal products administered for short time (up to 7 days) fixed durations of follow up might be more appropriate while for drugs administered for longer than 6 months, events driven study designs are likely to be more suitable and relevant.

If cardiovascular mortality is chosen as the primary endpoint, all-cause mortality should be a secondary endpoint. It is important that applicants should be prepared to inform about longer term outcome especially all-cause mortality (see also Section 7 on Safety) even when short term outcomes (e.g., symptoms or clinical status) are used as primary endpoints.

4.1.2. Short term outcomes (symptoms)

For products with short term administration (≤ 7 days), symptomatic improvement might be acceptable as primary endpoint. Symptoms should be carefully assessed under standardised conditions and at specified time points. Change in background therapy alone cannot be accepted as a surrogate for symptomatic improvement.

When symptoms either singly or as a composite (with clinical status) are chosen as primary endpoints in pivotal trials, it will be necessary to provide evidence that longer term outcomes such as mortality are not adversely influenced. This could be achieved in the same pivotal trial pre-authorisation or within the development programme utilising a combination of studies (see Section 7 on safety).

4.1.2.1. Dyspnoea

Dyspnoea (breathlessness) remains the most prominent symptom in the majority of patients with AHF and therefore, improvement in dyspnoea is a reasonable endpoint provided that issues related to timing of measurements and measurement tools are taken into account. Often it is claimed that this parameter (dyspnoea) is difficult to measure reliably, but such difficulties are attributable to poor technique, poor timing and insufficient effort to separate the impact of other confounding factors [3]. These pitfalls in the assessment of dyspnoea should be carefully avoided if this is chosen as an endpoint. Timing of the assessments to demonstrate persistent improvement (usually at 6 hours and thereafter, until at least 24 hours after initiation and termination of investigative therapy) is an important aspect that should be addressed and specified in the study protocol. This potentially avoids the inconsistencies that arise with the use of dyspnoea as an endpoint at one single time point.

Improvement in dyspnoea should be supported by improvement in clinical signs of congestion [3] or global clinical status change (see also sections 4.1.3, 4.2.7 and 4.2.8).

Various gradings for dyspnoea have been used in AHF trials. These often utilise scoring systems (grading from improved, no change and worsened compared to baseline) in a 3-point, 5-point or 7-point scale. VAS scales or scoring systems such as the 7-point Likert scale have been the most widely used measures of dyspnoea in AHF (or AHFS) trials. Other dyspnoea evaluation scales such as BDI (Baseline Dyspnoea Index) and TDI (Transition Dyspnoea Index) may also be useful but need proper validation in the setting of AHF. Any method chosen should be justified and defined a priori.

There is increased use of responder analysis or use of categorical composites to define improvement in dyspnoea i.e. when patients are categorised into groups based on response (for example: improved, unchanged or worsened). When categorical composites are converted into a scoring system using arbitrary weighting of each component and the components have markedly different implications for clinical benefit, it is particularly challenging to discern the overall effect, especially for regulatory

decision making. The relevance and impact of such analysis and, their discriminatory value should be defined *a priori* in order to ensure that the responder analysis is sensitive or reflective of changes in pathophysiology.

4.1.2.2. Other symptoms/signs

General well-being, quality of life and symptoms such as fatigue and mental confusion are important in patients with AHF but may be difficult to evaluate. A global assessment of the patient's clinical status (that includes both investigator- and patient' own evaluation of clinical status) may give useful complementary information to the assessment of dyspnoea (see also 4.1.3 and 4.2.8).

When the effects on pulmonary capillary wedge pressure (PCWP) or other haemodynamic parameters are evaluated in early phase studies, investigator or sponsor awareness of such effects may jeopardise blinding and thus influence the evaluation of symptoms. This awareness should be avoided, especially when these haemodynamic parameters are included as endpoints (co-primary or other) in the same (early phase) study.

4.1.3. Co-primary endpoints or composite endpoints

In general, in AHF trials, there is often use of co-primary endpoints and these may include various combinations of symptoms, signs, and of mortality or morbidity. It is expected that co-primary endpoints are clinically relevant measures and their choice is related to the pharmacological effect of the agent under investigation and the anticipated benefit. When symptoms and mortality are used as co-primary endpoints, care should be taken to ensure that the time of measurement and duration of the trial are appropriate. Dyspnoea and changes in clinical signs of congestion or objective assessment of global clinical status might be useful as co-primary end points under certain circumstances. Combination of dyspnoea and changes in PCWP as co-primary endpoints will need correlation with clinical events or survival and is likely to be of use only in early phase or exploratory studies. It is recognised that haemodynamic measurements are not routinely included in Phase III trials and their use in pivotal studies is not encouraged.

Use of composite measures as primary endpoints has increased over the years and their use in AHF trials necessitates consistency in the components. Composite endpoints should ideally consist of objective clinical events and the components should demonstrate directional concordance. For example, death (all cause or CV) and readmission for AHF might serve as a composite endpoint where the hospital readmissions are heart failure related, with pre-defined criteria. These readmissions may need to be adjudicated. A composite of major adverse cardiovascular events (MACE) could also be considered as a primary endpoint depending on the aetiology of AHF but with use of consistent definitions. Diverse and disparate measures would not be acceptable as components of a composite endpoint. Composite endpoints that use a mix of soft measures and objective clinical events introduce significant difficulties in weighting these appropriately and introduce statistical difficulties. There is additional complexity when components of the composite are directionally discordant.

4.2. Secondary endpoints

4.2.1. Cardiac and non-cardiac deaths

Cardiovascular death is an important endpoint especially when all-cause mortality is the primary endpoint in the pivotal trial(s). This might include sudden cardiac death, death due to myocardial infarction, documented arrhythmic death and death due to worsening of heart failure. Death due to

embolism and/or cerebrovascular accidents (strokes) is also a valid secondary endpoint and may be relevant for certain medicinal products. When the primary endpoint is dyspnoea in the short-term trials (days to weeks), mortality (preferably all cause) should be a secondary endpoint with similar time points of evaluation as when mortality is evaluated as a primary end point (for example, in hospital, 14 days, 30days or 60 days).

4.2.2. Hospitalisation

Duration of hospital stay during index admission may serve as an important secondary endpoint. This should include number of days in intensive/coronary care units (CCU) and total in-patient stay. Time to step down in care (from intensive/CCU) and time to discharge are other useful secondary endpoints. In certain cases, time to first hospitalisation after discharge of the index admission could also be used as a secondary endpoint. Visits to the emergency room when specifically due to a heart failure related event that necessitates rescue intervention could serve as a secondary endpoint. The number of re-hospitalisations (all cause, cardiovascular or heart failure hospitalisations (HFH)) is often useful as a secondary endpoint. When any of the above is included as a secondary endpoint, their definitions and criteria used for evaluation should be standardised and included in the protocol. Such events may require central adjudication.

Despite the clinical relevance of HFH, its use as an endpoint remains difficult and controversial. There is a need to objectively define HFH if it were to be used as an endpoint. Efforts must be put in place to differentiate HFH from those due to non-cardiovascular co-morbidities as well due to a CV cause but not primarily due to heart failure must be noted. In patients presenting with acute coronary syndrome (ACS) and heart failure, the follow up events should be classified as “HF related” or “non-HF related”.

With “time to an event” endpoints such as hospitalisation or first hospitalisation, heart transplant or death, it is important to carefully consider use of appropriate analytical methodology in dealing with competing events (for example, where observation of an event of interest may be prevented or hampered by other preceding events).

4.2.3. Worsening Heart failure (WHF)

In a subset of patients with AHF (or ADHF), several trials have used worsening heart failure (WHF) as a secondary end point. It is noted that there is inconsistent definition of WHF and often a small variation in the diuretic dose has been used to define this entity. There is also a potential for variability of definitions based on investigator experience. Such definitions are inadequate and unacceptable.

If WHF is used as a secondary end point or as a part of a composite primary end point, clear criteria would be necessary to define this event to reduce regional or investigator variability and events may need to be adjudicated. The criteria for WHF should be pre-specified in the protocol to achieve consistency. They should be clinically relevant and preferably include objective parameters such as need for mechanical ventilation including positive pressure ventilation and use of pre-defined rescue therapy.

4.2.4. Days alive and out of hospital

It has often been argued that this endpoint is important and provides valuable information about the wellbeing of the patients complementary to the number of re-hospitalisations. It includes three components, i.e., duration of the index hospitalization, duration of any repeat hospitalization, and all-cause mortality over a defined timeframe. However, this is a complicated endpoint as early deaths usually carry a greater weight than recurrent hospitalizations followed by a late death. So, this

endpoint may be most useful in particular subsets of patients who are hospitalised for a considerable period of time. One pre-requisite for this would be to ensure that the information on hospitalisation and rehospitalisation is sought actively and not assumed and the algorithm for evaluation) is pre-defined and analysis pre-specified.

4.2.5. Recurrent ischaemic events

In patients with AHF due to myocardial ischemia/infarction, reduction in ischaemic events (e.g. recurrent myocardial infarction, need for intervention) could be a secondary endpoint.

4.2.6. Haemodynamic measurements

Evaluation of haemodynamic parameters particularly PCWP might be useful in early phase studies for defining the pharmacodynamic (PD) effects of the agent, as well as to evaluate effects of therapeutic intervention. In the context of new inotropic drugs, evaluation of drugs' effect on the invasive haemodynamic parameters is considered important at some stage in the clinical development. However, in pivotal/confirmatory trials, patients may be included without these invasive measurements. Reduction of PCWP has not been proven to be useful or representative and is not an acceptable surrogate endpoint for clinical outcome or survival. Therefore, PCWP and other measurements such as blood pressure (BP), cardiac output (CO), cardiac index (CI), systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) would only be useful as secondary endpoints or, as co-primary end points in early phase trials. Use of haemodynamic measurements as sole primary endpoints in phase II-III studies is not recommended.

4.2.7. Changes in signs of congestion

Objective measures of changes in signs of congestion including radiology (chest X-rays) are important additional measures of efficacy and serve as supportive measures when used with dyspnoea or other symptoms to demonstrate short term efficacy. These include signs of pulmonary congestion, pleural effusions, cardiac silhouette and cardiothoracic ratio, pedal oedema, hepatic enlargement, raised jugular venous pressure and other physical signs.

4.2.8. Quality of life/global clinical status

Improvement in quality of life (QoL) and/or patients' self-assessed global clinical status, based on validated ordinal measures of response relative to baseline, could be used as secondary endpoint. It is important that the questionnaires or scales be validated for use in the setting of AHF. Investigator assessed global clinical status could also be used as secondary measure (endpoint) but will need to be evaluated in conjunction with patient reported outcome(s) to avoid bias.

4.2.9. BNP and NT-pro-BNP

Reduction in the levels of B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-pro BNP) could serve as a biochemical marker supportive of efficacy provided that they are part of the patient selection and inclusion (see Section 5 -Patient selection and stratification) with a well-defined cut off point. These peptides, at present, are most useful for their negative predictive value at baseline (see Section 5.3.1) for exclusion of heart failure. They may be used for monitoring patients' response in clinical management however with the caveat that link with a medicinal product's effect has not yet been established. In pivotal trials, neither of these peptides will serve as primary endpoints (singly or

in combinations) based on the current level of scientific knowledge and evidence base. Their value as surrogate endpoint is unproven.

4.2.10. Indices of renal function

Indices of renal function (such as blood urea and creatinine, creatinine clearance and glomerular filtration rate (GFR)) at admission and their subsequent change in response to therapy are known to reflect as well as influence the overall effects of many agents used in treatment of heart failure. They could be used either as stratification parameters and/or as secondary endpoints. This is likely to be dependent on the class and mode of action of the investigational agent. Agents that specifically improve renal function may have a different influence and may need specific trial designs and endpoints. These parameters do not have sufficient evidence base to function as primary endpoints at this point in time in confirmatory trials. Indices such as levels of cystatin-C may be included as exploratory endpoints, but are unlikely to serve as independent measures of efficacy at this point due to limitations in current knowledge and evidence base.

4.2.11. Other objective measurements

Changes in concomitant medication, oxygen therapy or intubation/assisted ventilation could be useful as secondary endpoints.

Enhanced diuresis may indicate improvement in organ perfusion and could serve as a secondary endpoint. There is however a caveat in that excess diuresis is likely to worsen renal function parameters. Therefore, for vasodilators and diuretic agents, change in organ function such as renal function often serves as a safety endpoint i.e. significant worsening of renal function during hospital stay and in the post discharge period should be recorded as a secondary endpoint, especially if it does not show improvement in the early post discharge period (see Section 4.2.9).

In case of low output or cardiogenic shock the use of measures of tissue perfusion (serum creatinine, lactate, SGOT, SGPT and venous or arterial O₂ saturation) could be considered as supportive evidence for efficacy.

5. Patient selection and stratification

In general, patients should be selected according to the proposed indication, the pathophysiological mechanism targeted and the mode of action of the agent under investigation. The patients included in the trials should be representative of the target population and the protocol should ensure a certain degree of homogeneity of clinical characteristics is expected. Excessive heterogeneity could result in equivocal or negative results or lead to post hoc subgroup analyses that are difficult to interpret. An increase in sample size alone may not resolve issues of heterogeneity. AHF due to ACS and ADHF may need to be studied separately. If patients from different categories are included in the same single trial, stratified randomisation, planned sub-group analysis with evaluation of directional concordance and consistency of effects might be necessary. When targeted groups are included or a stratification policy is adopted, they will need to have sound pathophysiological justification.

Patients who are hospitalized for heart failure ([HFH], see Sections 1 and 4.2.2) fall into a category that warrants consideration for inclusion into heart failure trials. It may be possible to include such patients in AHF trials with well-defined criteria that permit evaluation of the appropriate end point (for example mortality or recurrent events). When hospital stay is prolonged and there is worsening of heart failure after stabilisation of the acute admission (48-96 hours or just before discharge), these

patients might be considered for inclusion in trials of CHF (see *CHMP Note for Guidance on the Clinical Investigation of Medicinal Products for the Treatment of Cardiac Failure (CHMP/EWP/235/95, rev. 1)*).

SBP, renal function and the underlying aetiology have been noted to influence not only efficacy but also the overall outcome of the trial depending on the PD mechanism. Even in the absence of shock (e.g. due to acute MI), admission SBP has been recognised to influence the outcome of the trial. Renal function at admission and its progression through to post discharge period could impact the outcome of the trial. It is therefore important to aim at the appropriate target population depending on the pharmacology of the agent in question. For example, inclusion of subjects with low baseline BP in a vasodilator trial or those with evidence of ischaemia in trials of inodilators or contraction enhancers in might affect the results and conclusions. If these subpopulations/ subgroups are indeed included, attempts should be made to evaluate the effects appropriately using a well-defined stratification process.

Sponsors should justify the specific population selected for the study (or studies) and stratification plan or parameters. In order to ensure applicability of results to the European population, in any multinational trial, the standard of care should be representative for European practice. Also, heart failure increases with age [5-7] and therefore, the database should include a representative number of patients >65 years and >75 years in the therapeutic confirmatory studies (see also Section 7.3 Cardiac events [including myocardial injury]).

Patients should be selected for inclusion into trials using the following criteria:

5.1. Signs and symptoms

Shortness of breath is the predominant symptom in AHF and may be accompanied by confusion or disorientation. In those with acute exacerbation/worsening of pre-existing chronic congestive heart failure, other associated features such as fatigue, fluid retention and weight gain might be more prominent. Features of congestion evaluated using established parameters.

Physical signs of cardiac decompensation should also form part of the inclusion criteria and diagnosis of AHF. Signs of congestion would be crucial both for diagnosis and establishing a baseline in studies that use symptoms/signs as primary endpoints. Chest X-ray is helpful for the diagnosis and classification of AHF and the presence of pulmonary oedema/pulmonary congestion. Electrocardiogram (ECG) gives additional information regarding aetiology and diagnosis.

The admission SBP is a vital factor and could be used as a criterion for inclusion with a cut off level defined a priori. Admission SBP could also be used as a stratification factor with the proviso that subgroups are adequately powered to enable assessment of consistency of effect.

5.2. Haemodynamic abnormalities

Invasive haemodynamic assessments are often helpful to confirm the diagnosis of AHF. Commonly used haemodynamic parameters are: PCWP, cardiac output, right atrial pressure, systemic or pulmonary vascular resistance and many might be useful in early phase studies as inclusion criteria. For example, PCWP and right atrial pressure with pre-defined cut off values could be used for reducing heterogeneity of the patients included. In the context of new medicinal products, evaluation (using invasive or non-invasive methods) of medicinal products' effect on the haemodynamic parameters is considered important at some stage in the clinical development. When non-invasive methods are used, their validation will be important.

5.3. Cardiac dysfunction

Echocardiography will provide useful information regarding ventricular dilatation (left ventricular dimensions), left ventricular dysfunction, cardiac output and identify valve disease all of which are likely to influence outcome. Alternatively, left ventricular dysfunction could be measured by ventriculography or radionuclide scintigraphy. It is necessary to differentiate patients with systolic dysfunction (ejection fraction <40%; HFrEF) and those with preserved systolic function (ejection fraction >50%, HFpEF), as the progress of the disease and prognosis of those with preserved systolic function may differ from those with reduced systolic function [4]. Of note, the exact cut off point for distinction between these groups is a grey area (EF 40% or 45%), but consistent definitions should be used throughout the development programme. If both HFrEF and HFpEF groups are included in the same trial, a stratified randomisation is recommended. It is expected that criteria for inclusion will be clearly defined in the trial protocols and the same method of evaluation will be followed throughout the trials to permit comparisons.

In certain situations, MRI scans might prove to be of added value in determining cardiac anatomy and correlate with morphological alterations. The use of MR techniques is on the increase for evaluation of both anatomical and functional correlates and often the technique of choice for quantification of fibrosis, LV remodelling and LV mass which could prove useful in a heart failure trial. This however is not a mandatory investigation.

5.3.1. BNP and NT pro-BNP

Assessment of natriuretic peptides (BNP or NT pro-BNP) at present is most useful for their negative predictive value in the diagnosis of AHF and could be used as entry criteria (i.e. for inclusion/exclusion of patients) provided that cut off values for both BNP and NT pro-BNP are defined "a priori". Use of BNP or NT pro-BNP for stratification or for prognosis cannot be recommended at this point in time. However, their levels may be used as exploratory/ tertiary end points for evaluating the effect of the intervention.

5.4. Renal function

Changes in renal function in response to therapy could also affect the overall risk/benefit of the agent. Inclusion of an adequate number of subjects with different levels of renal function to permit subgroup analysis is encouraged. As most trials have so far excluded patients with severe renal impairment, adequate numbers of those with moderate renal dysfunction should be included or investigated in the clinical development programme as a minimum.

6. Study design

It is acknowledged that the conduct of clinical trials in AHF patients presents a challenging task.

6.1. Human Pharmacology studies

Human pharmacology studies are unlikely to be different to those described for patients with CHF. For details of regulatory expectations and requirements, reference is made to the *CPMP Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Cardiac Failure (CPMP/EWP/235/95 Rev. 1)*.

6.2. Early therapeutic studies (and dose finding studies)

When early clinical pharmacology studies are carried out in healthy volunteers only, pharmacokinetic (PK) and PD modelling would be expected in patients with AHF in order to evaluate the possible effects of altered exposure. The dose ranging studies should be performed in patients close to the target clinical indication and may include haemodynamic data among others. The most appropriate design would depend on the characteristics of the medicinal product and the intervention in question. Forced dose escalation studies will provide the basis for any dosing recommendations and also the maximum tolerated dose. This can be tested further in parallel dose response studies using a fixed-doses design or, if deemed safer, titrated gradually to the therapeutic dose in accordance with *ICH E4 Dose Response Information to Support Drug Registration (CHMP/ICH/378/95)*. Attempts should be made to determine the minimum effective dose, the dose escalation or titration sequence and the maximum duration of treatment based on response noted in haemodynamic parameters, symptoms and safety.

The proof of principle studies in subgroups should be planned and specified *a priori* and *post hoc* manipulations should be minimised.

Early phase therapeutic studies should also evaluate the potential for PK and PD interactions with other agents used concomitantly in AHF.

6.3. Pivotal therapeutic studies

Phase III studies are expected to be double blind and randomised. The absence of double blinding may compromise the interpretation particularly of symptom-based studies where subjective elements may dominate.

Placebo controlled studies are required if the new medicinal product is intended as add-on therapy to current conventional treatment and belongs to a new therapeutic class or to a therapeutic class which has not previously been considered for the treatment of AHF. Sponsors should ensure that patients receive appropriate background therapy in accordance with clinical guidelines. The absence of placebo-controlled studies in these situations will need to be justified.

The choice of the active comparator used in the pivotal trial is dependent upon the class and the haemodynamic effects of the new drug. For vasodilators, nitroglycerine or nitroprusside are the preferred comparators, while furosemide and dobutamine could serve as the appropriate (most widely used) comparators for diuretics and inotropes respectively. The choice of comparators should be appropriately justified. If the new medicinal product belongs to an existing therapeutic class, a double blind, randomised, active comparator controlled study against another licensed product of the same therapeutic class is expected.

There may be agents used commonly in clinical practice that do not specifically have an approved indication for heart failure in Europe and comparison to such an agent may require additional justification. In these instances, the trial should preferably aim to establish superiority and non-inferiority trials might not be sufficient for approval. When a hypothesis of non-inferiority is the selected approach, underestimation of any difference between treatments should be avoided and an adequate demonstration of assay sensitivity must be ensured. Inclusion of a placebo arm would serve this purpose.

The duration of therapy will depend upon the class, type and route of administration of the drug under development. When administered as an intravenous infusion, duration usually varies from 6 - 48 hours but may occasionally be required for longer than 48 hours. The duration of administration in the trial should be justified in the study protocol.

The duration of the trial is dependent on the duration of therapy proposed and the expected benefit. A longer follow-up may be needed to ensure safety (see Section 7.1 Mortality).

6.3.1. Dosage

Dose response should be adequately studied in early phase studies and the choice of the dose for the pivotal comparison will need to be adequately researched and supported by data. Choosing doses based on haemodynamic parameters only is often a risky strategy as the link between changes in haemodynamics and outcome measures may be tenuous. Therefore, the choice of the dose in pivotal studies is expected to be based both on haemodynamics, signs and symptoms, patient reported outcomes and tolerability. The dose may need to be adjusted (up-or down-titration); such adjustments should be pre-specified including timing of such alterations based on data from earlier studies.

In active comparator trials, appropriate licensed doses of the comparator should be used. Use of doses not authorised in the EU for the comparator might not be acceptable and would need to have strong justification and biological rationale.

6.3.2. Concomitant medication

The use of concomitant therapy should in all cases be optimised and predefined in the study protocol. The information on the use of concomitant drugs should be carefully documented and its potential impact on the effect of the drugs under study assessed. Patients already on medications such as ACE-inhibitors, beta-blockers, digoxin, diuretics etc., should continue to receive these medications unless contraindicated in view of an acute situation or unless decided otherwise by the attending physician. Changes in concomitant medications or dose of concomitant medications could be useful information as part of the overall evaluation of improvement and should be carefully documented. Unscheduled or unplanned changes during the study should be kept to a minimum.

7. Evaluation of Safety

The size of overall safety database will depend on the class of the drug and the indication sought and the target population. The safety database for each group of patients grouped by indication should be adequate or large enough to exclude any potential increase in mortality with the use of the agent (e.g. if a claim is made for patients with ADHF or AHF due to ACS, the database in either group must be adequate to make this judgement). It would also be expected that the database is of adequate size to evaluate any imbalance arising from use of concomitant medications that could confound evaluation and interpretation of outcomes.

7.1. Mortality

The safety issues that are of interest include life threatening arrhythmias, ischaemia and hypotension leading to increased mortality. Even if the claim is made for symptomatic benefit only, mortality data for the hospitalised period, end of 30 days period and over six months are expected to be available in the database in order to exclude the possibility of any deleterious effect. Such data could arise either from several trials or alternatively within the pivotal study by the use of all-cause mortality as co-primary end point to symptoms with a well-defined and acceptable non-inferiority margin. The choice of the time point to establish lack of harm will be dependent on the duration of the drug administration and the characteristics of the patient population in the safety dataset. In principle, assuming a comparison against a placebo or standard of care (SOC), evidence for exclusion of harm in AHF patients using a pooled approach could be an upper bound of the 95%, two sided confidence interval

below 1.8 in the event that HR is approximately 1. For active comparators, these may differ and will need an “a priori” discussion with the regulatory agencies and request for scientific advice.

7.2. Haemodynamic effects and related symptoms

The occurrence of tachycardia, hypotension and headache should specifically be reported. Evaluation of hypotensive episodes with vasodilators is an important aspect and should be defined in the protocol. Standard definitions for hypotension should be used. In certain cases, specific definitions may be necessary for example when BP is used as a stratification parameter.

7.3. Cardiac events (including myocardial injury)

Major ischaemic events and occurrence of arrhythmias should carefully be documented as there is a close link between myocardial injury and outcome in heart failure. Such monitoring is crucial in ACS with AHF, or when inotropic agents are studied. Evaluation should include 12-lead ECGs and Holter monitoring. Measurement of myocardial injury before discharge by troponin or other suitable biomarker may be of value as a safety measure. It is important to carefully monitor for any possibility of QTc prolongation (alteration in cardiac repolarisation) in addition to evaluation of QT/QTc, during early drug development.

Patients at special risk e.g. older patients, females, patients with diabetes/hepatic disease should be observed for any exaggerated pharmacological response. This applies in particular to older patients (> 65 years and >75 years) as additional safety considerations should be taken into account, such as reduced renal reserve or incipient renal or hepatic impairment, reduced compensatory ability for excessive vasodilatation and increased incidence of arrhythmias such as atrial fibrillation⁵.

7.4. Renal function

Assessment of indices of renal function (e.g. blood urea, serum creatinine, proteinuria etc.) is important as changes in renal function may influence the outcome. Special attention should therefore be paid to this aspect with adequate evaluation in the clinical trials. Significant alterations in these parameters during treatment, new development of renal insufficiency and need for initiation of dialysis are important safety issues. These data collected prospectively should be provided in addition to 30 days and 6 months mortality data. The follow up period in which these were collected should be clearly defined and specified.

8. Special populations (older patients)

Acute heart failure (and AHFS) is a disease essentially of the older people with increasing prevalence as age advances as evidenced by the mean age of ~70-72 years in majority of the studies to date. Continued attention is necessary to ensure that older subjects are adequately represented in the studies, with due attention to issues relating to therapeutic choices, fitness to participate in the trial and overall general health (see efficacy and safety sections).

List of Abbreviations

| | |
|------|-----------------------------------|
| AcMI | Acute myocardial infarction |
| ACS | Acute coronary syndrome |
| ADHF | Acute decompensated heart failure |
| AHF | Acute heart failure |

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|------------|---|
| AHFS | Acute heart failure syndromes |
| BNP | B-type natriuretic peptide |
| CHF | Congestive heart failure |
| CHMP | Committee of Human Medicinal Products |
| CI | Cardiac index |
| CO | Cardiac output |
| ECG | Electrocardiogram |
| EF | Ejection Fraction |
| EWP | Efficacy working party |
| HF | Heart failure. |
| HFH | Heart failure hospitalisation. |
| HFpEF | Heart Failure-preserved ejection fraction |
| HFrEF | Heart Failure-reduced ejection fraction |
| ICH | International conference on Harmonisation |
| MACE | Major adverse cardiovascular events |
| NT-pro-BNP | N terminal pro-BNP |
| PCWP | Pulmonary capillary wedge pressure |
| PVR | Peripheral vascular resistance |
| QoL | Quality of life |
| SBP | Systolic blood pressure |
| SVR | Systemic vascular resistance |

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