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8 This guideline replaces addendum CPMP/EWP/2986/03 "Note for guidance on clinical investigation of
9 medicinal products for the treatment of cardiac failure – addendum on acute cardiac failure".

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

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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 Note for Guidance on the Clinical Investigation of Medicinal Products for the Treatment of Cardiac Failure (CHMP/EWP/235/95, rev. 1) provides limited regulatory guidance for development of medicinal product for the treatment of acute heart failure and led to the addendum on acute heart failure (CHMP/EWP/2986/03). The current document is a revised version of this addendum and is intended to provide updated guidance on the evaluation of drugs in the treatment of Acute Heart Failure (AHF) on those aspects that are not adequately covered in the guideline on chronic heart failure. The text has been updated in relation to the factors in particular patient characteristics that impact outcome of AHF trials and their evaluation. This guideline provides main regulatory considerations and requirements for the development of a medicinal product for the treatment of acute heart failure.

1. Introduction (background)

Acute Heart Failure represents a very heterogeneous group of patients with certain common features. It is characterised by a rapid onset of a wide spectrum of symptoms and signs, accompanied by haemodynamic abnormalities and neuroendocrine activation that arise secondary to abnormal cardiac function. The term acute heart failure (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). The most common clinical entity encountered is acute exacerbation of chronic heart failure that was previously controlled with therapy and is often termed "acute decompensated heart failure (ADHF)".[1] Other causes of acute heart failure include acute coronary syndrome (ACS), valvular heart disease, and severe hypertension. Acute onset atrial fibrillation or other atrial arrhythmias may be contributing factors in precipitating AHF. AHF may also occur in the peri-operative setting including both cardiac and non-cardiac surgery. Of note, acute heart failure may be related to systolic or diastolic dysfunction or to a mismatch between preload and afterload. Isolated acute right 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 of AHF include acute decompensated heart failure, pulmonary oedema and cardiogenic shock. The pathophysiology differs considerably between these entities which are likely to influence the type of intervention planned and the clinical trials needed to investigate such interventions or treatments. There are however, aspects to the treatment of AHF that are common in all and include rapid relief of congestion, improvement in haemodynamic status, correction of the underlying cause and reduction in mortality. Differences in the aetiology, pathophysiology and clinical manifestation at presentation will influence the relative order, importance and application of particular interventions and determine the design of the studies used to evaluate drugs for AHF (AHFS). Moreover, as patient characteristics are likely to differ, patient selection and criteria for inclusion will need to be tailored. In this context, perioperative acute heart failure should be studied as a separate entity as the symptoms cannot be assessed and other clinical parameters should be used.

The current interventions used for acute heart failure include pharmacological treatments, non-pharmacological interventions, and surgery such as heart transplant or ventricular assist devices.

2. Scope

This document (guideline) 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 mechanical devices to provide mechanical support, are not within the scope of this document.

3. Legal basis

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 outline 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)
- Guideline for Good Clinical Practice (ICH E6)
- Dose-Response Information to support Drug Registration (ICH E4)
- Statistical Principles for Clinical Trials (ICH E9)
- Choice of Control Group and Related Issues in Clinical Trials (ICH E10)
- Points to Consider on Switching between Superiority and Non-inferiority (CHMP/EWP/482/99)
- Note for Guidance on the Investigation of Drug Interactions (CHMP/EWP/560/95)
- Studies in Support of Special Populations: Geriatrics (ICH E7 CHMP/ICH/379/95) and related Q&A document (EMA/CHMP/ICH/604661/2009)

4. Evaluation of efficacy

Therapeutic measures utilised in AHF aim to relieve symptoms, and/or reduce mortality and morbidity. Understandably, evaluation of efficacy will depend on the pharmacological profile and mechanism of action of the drug, and the expected benefit. However, it is recognised that the overall efficacy of a drug or intervention in AHF/AHFS is significantly influenced by the patient's clinical profile at presentation, the aetiology and the precipitating factor of AHF. Based on data from recently completed trials, several features have been noted to significantly influence not only efficacy but also the overall outcome of the trial. These include systolic blood pressure at admission, renal function and the underlying aetiology. Even in acute decompensated heart failure (where shock is not common unlike that due to acute myocardial infarction (AcMI)), admission systolic blood pressure has been recognised to influence the overall benefit risk. Similarly, admission renal function and its progression through the hospital admission to post discharge period influence the overall benefit risk ratio.

For demonstration of efficacy, the measures utilised will depend on the drug in question, the aetiology of heart failure and the constellation of symptoms. The underlying mechanisms of action may be to improve haemodynamics, induce diuresis or reduce fluid overload, or to limit unfavourable neuroendocrine activation and, therefore influence the endpoint used and the timing of measurement. Usually, it is expected that improvement either in terms of survival or symptoms or quality of life will be shown and these could be short term or long term measures. Short term measures would mainly rely on consistent improvement in symptoms including dyspnoea and improved signs of congestion. The main longer term measure of efficacy would be mortality as this 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 BNP or NT-pro BNP. Different measures of efficacy might be applicable depending on the aetiology of acute heart failure. For example, in AHF following ischemic events or acute MI, short term mortality at 30 days or at discharge are likely to be the crucial measures for an agent administered for short term. When longer term administration of the agent is the aim, the time of evaluation of efficacy will be longer.

It is recognised that with globalisation of clinical trials, there is likely to be a need to address the issue of consistency and uniformity in characteristics of patients recruited in to the trial. Variations exist in clinical practises, clinical guidelines or local treatment preferences, and these might inadvertently influence the overall result.[2] It is expected that these aspects will be carefully considered within the development programmes to limit excess heterogeneity. Efforts should be made to standardise baseline characteristics and treatments as much as possible within the context of the representativeness of the trial population for the actual situation.

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 which will influence the choice of the primary endpoint in clinical trials. The choice of the endpoints may also depend on the pharmacological profile and mechanism of action of the drug.

4.1.1. Mortality

The preferred primary endpoint is all cause mortality. As the treatment for acute heart failure is often short term administration of the investigational agent (drug), these would either be:

- in-hospital mortality during the index admission
- mortality at 30 days

Longer term outcome such as 6 months or 1 year might also be relevant and could be included depending on the pharmacological profile of the drug, the duration of administration, and the patient population. Trial designs with finite endpoints are encouraged, whether short term or long term.

4.1.2. Short term outcomes (symptoms)

For short term trials, symptomatic improvement might be acceptable as primary endpoint provided no deleterious effects are shown as regards mortality. 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.

4.1.2.1. Dyspnoea

Dyspnoea (breathlessness) remains the most prominent symptom in the majority of patients with acute heart failure. Often it is claimed that this parameter 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. These pitfalls in the assessment of dyspnoea should be carefully avoided and not deter from inclusion of this endpoint for demonstration of symptomatic improvement. Therefore, improvement in dyspnoea is a reasonable endpoint provided that issues related to timing of measurements and measurement tools are taken into account.

Persistent improvement in dyspnoea (during the hospital stay) could serve as a primary endpoint if supported by improvement in clinical signs of congestion (see section 4.2.6).[3] Timing of the assessment to demonstrate persistent improvement is considered an important aspect that needs attention. This potentially avoids the inconsistencies that arise with the use of dyspnoea as an endpoint at one single time point and should be clearly specified in the study protocol (usually at baseline, at 6 hours and sequentially thereafter, until at least 24 hours after initiation of investigative therapy).

Various gradings for dyspnoea have been used in AHF trials. These often utilise scoring systems (grading from improved, no change and worsened) in a 3-point, 5-point or 7-point scale. VAS scales and 7-level Likert scale have been the most widely used measures of dyspnoea in AHF (AHFS) trials. Other dyspnoea evaluation scales such as BDI (Baseline Dyspnoea Index) and TDI (Transition

185 Dyspnoea Index) may also be useful but need proper validation in the setting of heart failure. Any
186 method chosen should be justified and defined *a priori*.

187 When the effect on mortality and morbidity is neutral, improvement in dyspnoea and changes in signs
188 of congestion supported by reduction in pulmonary capillary wedge pressure (PCWP), either from same
189 or different studies, might be acceptable as evidence of efficacy.

190 **4.1.2.2. Other symptoms/signs**

191 General well being, fatigue and mental confusion are also important symptoms in patients with acute
192 heart failure but may be difficult to evaluate. A global assessment of the patient's clinical status (that
193 includes both investigator and patient oriented evaluation of clinical status) may give useful
194 complementary information to the assessment of dyspnoea and could be used as co-primary endpoint
195 (see also 4.1.3).

196 If PCWP or other haemodynamic parameters are evaluated in early phase studies, investigator or
197 sponsor awareness of such effects may influence evaluation of symptoms and this should be carefully
198 avoided.

199 ### *4.1.3. Co-primary endpoints or composite endpoints*

200 In general, use of co-primary endpoints is preferred to composite endpoints. Co-primary end points
201 may include various combinations of symptoms or symptoms and mortality/morbidity. Use of
202 haemodynamics measurements as co-primary endpoint in pivotal trials is not encouraged.

203 Use of composite measures as primary endpoints has increased over the years and several have been
204 used appropriately in chronic heart failure. Composite endpoints should ideally consist of objective
205 clinical events and the components should demonstrate directional concordance. Of importance, it is
206 expected that the composite endpoints proposed <u>are well validated</u>. For example, death and hospital
207 readmission for acute heart failure might serve as a composite endpoint. The reasons for hospital
208 readmission should be related to heart failure and need to be fully adjudicated. A composite of MACE
209 (major adverse cardiovascular events) events could also be considered as a primary endpoint
210 depending on the aetiology of AHF.

211 Complex composite endpoints that include both objective (mortality/morbidity) and "softer or
212 subjective" measures such as symptoms (other than dyspnoea), quality of life, biochemical or
213 functional measures or changes in concomitant therapy make interpretation difficult and are
214 discouraged. This also includes use of "categorical composites" i.e. when patients are categorised into
215 groups based on response (for example: improved, unchanged or worsened). Such composite
216 endpoints, often a mix of soft measures and hard clinical events introduce significant difficulties in
217 weighting these appropriately and also introduce statistical difficulties. Diverse and disparate measures
218 would also not be acceptable as components of a composite endpoint.

219 ## *4.2. Secondary endpoints*

220 ### *4.2.1. Cardiac and non-cardiac deaths*

221 Cardiovascular deaths should be included as secondary endpoint. These might include sudden cardiac
222 death, death due to myocardial infarction, arrhythmic death and worsening of heart failure. Non-
223 cardiac or vascular death due to embolism and/or cerebrovascular accidents (strokes) is also a valid
224 secondary endpoint and may require evaluation. When the primary end point is dyspnoea, the use of
225 overall mortality (all cause mortality) as a secondary endpoint is encouraged.

226 ### *4.2.2. Hospitalisation*

227 Duration of hospital stay during index admission may be another secondary endpoint. This should
228 include number of days in intensive/coronary care units and total in-patient stay. Time to step down in

care and time to discharge may be other useful secondary endpoints. In certain cases, time to first hospitalisation after discharge of the index admission could also used as a secondary end point. When any of these are included as secondary endpoints, their definitions and criteria used for evaluation should be standardised and included in the protocol to reduce variability due to differences between trial sites and investigators. During long term follow-up of acute treatment, the number of rehospitalisations (all cause, cardiovascular or heart failure hospitalisations) should be considered an additional secondary endpoint as rehospitalisation rate over 6 months in acute decompensated heart failure patients may be as high as 50%.

4.2.3. 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 rehospitalisations. It is possible to use this as a secondary endpoint when these data have been collected systematically. One pre-requite for this would be to ensure that the information is sought actively and not assumed. Secondly, it is important to ensure that events are censured appropriately in order to avoid any confounding effect when mean and median data are presented.

4.2.4. Recurrent ischaemic events

In patients with acute heart failure due to myocardial ischemia/infarction reduction in recurrent ischemic events (e.g. recurrent MI, need for intervention strategies) could be a secondary endpoint.

4.2.5. Haemodynamic measurements

Use of haemodynamic parameters particularly PCWP might be useful as co-primary endpoints in early phase studies for defining the pharmacodynamic effects of the agent, as well as to evaluate effects of therapeutic intervention. Elevated PCWP has been shown, in some studies, to be predictive of sudden death and progressive decompensation and is often used as a short term measure of efficacy. In the context of new inotropic drugs, evaluation of drugs' effect on the haemodynamic parameters is considered unavoidable at some stage in the clinical development. However, in pivotal/confirmatory trials patients may be included without these invasive measurements. Reduction of PCWP is not an acceptable surrogate endpoint for clinical outcome/survival. Therefore, PCWP and other measurements such as blood pressure, CO, CI, SVR and PVR would only be useful as relevant secondary endpoints and the use of haemodynamic measurements as sole primary endpoints in phase II-III studies is not recommended.

4.2.6. Changes in signs of congestion

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

4.2.7. Other objective measurements

Changes in concomitant medication, oxygen therapy and 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 below).

In case of low output or cardiogenic shock the use of measures of tissue perfusion (serum creatinine, lactate, SGOT, SGPT and venous or arterial O_2 saturation) could be considered as supportive evidence for improvement.

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 acute heart failure. Investigator assessed global clinical status could also be used as secondary measure (endpoint) but will need to be evaluated in conjunction with patient reported QoL and global status to avoid bias.

4.2.9. BNP and NT-pro-BNP

Reduction in the levels of B-type natriuretic peptide (BNP) or NT-pro BNP (N-terminal 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) 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) and neither of these peptides will serve as stand alone endpoints or as part of a composite primary endpoint for measuring efficacy based on the current level of scientific knowledge and evidence base.

4.2.10. Indices of renal function

Indices of renal function (blood urea and creatinine) at admission and their subsequent change in response to therapy are known to influence the overall results of many agents used in treatment of heart failure. They could be used either as stratification parameters 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.

5. Patient selection and stratification

It is accepted that symptoms in acute heart failure develop within hours or days. It is also recognised that the overall efficacy of a drug or intervention in AHF/ AHFS is significantly influenced by the patient's clinical profile at presentation, the aetiology and the precipitating factor of AHF. Different relative weights may be placed on clinical, haemodynamic abnormalities and cardiac dysfunction by the clinicians involved in the management and their diagnostic judgement. 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. It is expected that these aspects will be carefully considered within the development programmes when selecting patients. Homogeneity of population is an important aspect and efforts should be made to ensure this both in the protocol and in practice. Excessive heterogeneity could result in equivocal or negative results or lead to post hoc subgroup analysis that are difficult to interpret. An increase in sample size may not be the solution to such issues. For example, depending on the indication, acute heart failure (due to AcMI and ACS) and acute decompensated heart failure may need to be studied separately. If patients from both categories are included in one trial, stratification into the subgroups so as to permit adequately powered sub-group analysis will be needed to explore consistency of effects. When targeted groups are included or a stratification policy is adopted, they will need to have sound pathophysiological justification.

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 multicentre trial, it is expected that approximately 25-30% of the population will be from Europe in order to be a representative sample. 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).

Patients will be selected for inclusion in to 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 congestive heart failure (CHF), other associated features such as fatigue, fluid retention, and weight gain might be more prominent. Features of congestion evaluated using established features and a chest X-ray should be part of the inclusion criteria.

Physical signs of cardiac decompensation should also form part of the inclusion criteria and diagnosis of acute heart failure. 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 confirmatory for the diagnosis and classification of acute heart failure and the presence of pulmonary oedema/pulmonary congestion. Electrocardiogram (ECG) gives additional information regarding aetiology and diagnosis.

One physical sign that has an important influence on the overall result is the systolic blood pressure at admission. Its impact is likely to be different with different classes of drugs and situations i.e. pathophysiology. The admission systolic blood pressure (SBP) could therefore be used as a criterion for inclusion with a cut off level defined *a priori*. Interestingly, admission SBP could also be used as a stratification factor for subgroup analysis, with the proviso that such an analysis is adequately powered.

5.2. Haemodynamic abnormalities

Invasive haemodynamic assessments are often helpful to confirm the diagnosis of acute heart failure. Commonly used haemodynamic parameters are wedge pressure (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 inotropic drugs, evaluation of drugs' effect on the haemodynamic parameters is considered unavoidable at some stage in the clinical development.

5.3. Cardiac dysfunction

It is necessary to differentiate patients with systolic dysfunction (ejection fraction <40%) and those with preserved systolic function (EF >40%). Echocardiography is likely to provide useful information regarding ventricular dilatation (left ventricular dimensions), left ventricular function (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 distinguish and stratify patients based on their cardiac function as the prognosis of those with preserved systolic function is likely to be different to those with systolic dysfunction.[4] If both systolic and diastolic dysfunction groups are included in the same trial, a stratified randomisation is recommended. It is expected that echocardiographic criteria for inclusion will be clearly defined in the trial protocols.

5.3.1. BNP and NT pro-BNP

Assessment of B-type natriuretic peptide (BNP) at present is most useful for negative predictive value in the diagnosis of acute heart failure 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 can not be recommended at this point time.

362 ### *5.4. Renal function*

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

368 ## 6. Study design

369 It is acknowledged that the conduct of clinical trials in this group of patients presents a challenging
370 task.

371 ### *6.1. Human Pharmacology studies*

372 Human pharmacology studies for a product to be used in patients with acute cardiac failure are unlikely
373 to be different to those described for patients with chronic cardiac failure. For details of regulatory
374 expectations and requirements, reference is made to the CPMP Note for Guidance on Clinical
375 Investigation of Medicinal Products for the Treatment of Cardiac Failure (CPMP/EWP/235/95 Rev. 1).

376 ### *6.2. Early therapeutic studies (as well as dose finding studies)*

377 When studies are carried out in healthy volunteers, pharmacokinetic and pharmacodynamic modelling
378 would be expected in patients. The dose ranging studies should be performed in patients close to the
379 target clinical indication and include haemodynamic data. The most appropriate design would depend
380 on the characteristics of the medicinal product and the intervention in question. Forced dose escalation
381 studies will provide the basis for any dosing recommendations and also the maximum tolerated dose.
382 This can be tested further in parallel dose response studies using a fixed dose or, if that seems safer,
383 titrated gradually to it in accordance with ICH E4 (CHMP/ICH/378/95). Attempts should be made to
384 determine the minimum effective dose, dose escalation or titration and the maximum duration based
385 on response noted in haemodynamic parameters, symptoms and safety.

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

388 Early phase therapeutic studies should also evaluate the potential for pharmacokinetic and
389 pharmacodynamic interactions with other agents used concomitantly in AHF.

390 ### *6.3. Pivotal therapeutic studies*

391 Phase III studies are expected to be double blind and randomised. The absence of double blinding may
392 compromise the interpretation of symptoms-based studies. This may then require harder clinical
393 endpoints (e.g. all cause mortality).

394 Placebo controlled studies are required if the new product is intended as add-on therapy to current
395 conventional treatment and belongs to a new therapeutic class or to a therapeutic class which has not
396 previously been considered for the treatment of AHF. In this scenario the efficacy of the new drug is
397 expected to be shown in placebo-controlled trials where the new drug/placebo is added to an optimised
398 background therapy well defined in the study protocol. Sponsors should ensure that patients receive
399 appropriate background therapy in accordance with clinical guidelines. The absence of placebo-
400 controlled studies in these situations will need to be justified.

In active controlled studies, 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. For diuretics, furosemide is the most widely used and hence the expected comparator for assessment of a new diuretic. Dobutamine, alone or in combination with dopamine or other vasoactive agents, is the most widely used inotrope in patients with acute heart failure. While these are the preferred comparators, alternative options may be available and the choice of other 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. 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.

The duration of therapy will depend upon the class, type and route of administration of the drug under development, ranging from a few hours to a few days. When administered as i.v 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 and the expected benefit in terms of improvement in symptoms and morbidity/mortality. A longer follow-up may be needed to ensure safety (see section 7.1).

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 should be based both on haemodynamics and patient reported outcomes. 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 comparative 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 ideally be optimised and, in all cases, 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 overall safety database will depend on the class of the drug and the indication sought. The safety database for each group of patients grouped by indication should be large enough to exclude a detrimental effect on mortality and morbidity (e.g. if a claim is made for patients with acute decompensated heart failure, the database in this group must be adequate to make this judgement).

7.1. Mortality

The overall safety database will depend on the class of the drug and the indication sought. The safety issues that could arise from the use of inotropic agents as concomitant medications in acute heart failure include life threatening arrhythmias, sudden death, ischaemia and hypotension. This could be a confounding factor if there is an imbalance between treatment groups in the use of such inotropes where increased mortality has been noted. 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 exclude the possibility of any deleterious effect, both short and long term.

7.2. Haemodynamic effects and related symptoms

The occurrence of tachycardia, hypotension, flushing 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 blood pressure 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 tropinin 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. elderly, females, patients with diabetes/hepatic disease should be observed for any exaggerated pharmacological response. This applies in particular to elderly 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 fibrillation[5].

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 and the period in which these were noted should be specified.

List of Abbreviations

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