20 July 2017
EMA/547655/2017
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on draft Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure (CPMP/EWP/235/95, Rev.2)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	De Hart&Vaatgroep
3	AstraZeneca Pharmaceuticals
4	EFPIA – Tiia Metiäinen (tiia.metiainen@efpia.eu)
5	Les Laboratoires Servier
6	Committee on Regulatory Affairs of HFA of ESC

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
1	The use of PROs is incorporated in the guideline, which is supported by De Hart&Vaatgroep. However, their use seems restricted: “PROs may include improvement of symptoms”, “PROs can be used as secondary outcomes” and “PROs should be considered as supportive”. De Hart&Vaatgroep is of the opinion that medicinal products should be judged by the extent to which they contribute to the reduction of the (individual) patient experienced limitations / symptoms and improve the patient desired quality of life, and that PROs should play an important role in this assessment. In 2015 in the Netherlands, in collaboration with field parties and insurers, PROs for Heart failure were developed and validated by the Netherlands institute for health services research Nivel, the CaReQol CHF. A unique feature of these PROs is that they were developed on input from heart failure patients and can therefore be very relevant for the development, assessment and evaluation of care and medicines / medical treatment. The CaReQoL can be used as an appropriate primary assessment measure, next to mortality and hospitalization. We are of course aware that not all symptoms and limitations can be treated with one single drug and that drug treatment should be part of integrated care.	Partly accepted. We agree that PROs are important supportive measures to be assessed in patients with heart failure but at the present they cannot represent an approvable primary end point. Furthermore, it is now requested that scales or scores can be used for the assessment of symptoms provided that they are validated in the populations (and in the languages) in which they are being tested (see section 5.4). The use of PROs as primary end point is not endorsed, unless used in combination with functional capacity under exceptional circumstances.

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De vragen op deze pagina gaan allemaal over chronisch hartfalen. Wilt u alstublieft géén vragen overslaan. Als een vraag niet op u van toepassing is, kunt u het meest rechtse vakje aankruisen (n.v.t.). *Vul de stelling in de donkere balk aan met de zinnen eronder.*

Door mijn hartprobleem...	**nooit**	**zelden**	**soms**	**vaak**	**altijd**	**n.v.t.**
...doe ik alles langzamer dan ik zou willen	❑	❑	❑	❑	❑	❑
...heb ik weinig energie	❑	❑	❑	❑	❑	❑
...is het moeilijk om spontaan iets te doen	❑	❑	❑	❑	❑	❑
...kan ik niet eten wat ik wil	❑	❑	❑	❑	❑	❑
De afgelopen twee weken...	**nooit**	**zelden**	**soms**	**vaak**	**altijd**	**n.v.t.**
...was ik bang dat er iets met mijn hart zou gebeuren	❑	❑	❑	❑	❑	❑
...sliep ik slecht door mijn hartprobleem	❑	❑	❑	❑	❑	❑
...voelde ik mij veilig door de zorg van het ziekenhuis	❑	❑	❑	❑	❑	❑
...had ik het gevoel dat elke dag de laatste kon zijn	❑	❑	❑	❑	❑	❑
Door mijn hartprobleem had ik de afgelopen twee weken...	**nooit**	**zelden**	**soms**	**vaak**	**altijd**	**n.v.t.**
...moeite met lopen	❑	❑	❑	❑	❑	❑
...moeite met fietsen	❑	❑	❑	❑	❑	❑
...moeite met mijn taken in het huis	❑	❑	❑	❑	❑	❑
...moeite om te genieten van mijn gezin	❑	❑	❑	❑	❑	❑
...moeite om met familie of vrienden om te gaan	❑	❑	❑	❑	❑	❑
...moeite om te genieten van het leven	❑	❑	❑	❑	❑	❑
Door mijn hartprobleem voelde ik mij de afgelopen twee weken...	**nooit**	**zelden**	**soms**	**vaak**	**altijd**	**n.v.t.**
...somber	❑	❑	❑	❑	❑	❑
...tot weinig in staat	❑	❑	❑	❑	❑	❑
...prikkelbaar	❑	❑	❑	❑	❑	❑
...angstig	❑	❑	❑	❑	❑	❑
Ten slotte...	**nooit**	**zelden**	**soms**	**vaak**	**altijd**	**n.v.t.**
Mijn zorgverleners houden mij goed in de gaten	❑	❑	❑	❑	❑	❑
Ik vertrouw er op dat medische hulp op tijd komt als er wat met mijn hart gebeurt	❑	❑	❑	❑	❑	❑
Ik vertrouw op de zorg die ik krijg	❑	❑	❑	❑	❑	❑

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3	Very good initiative to revise this guideline and change the whole perception on what matters in HF for drug development: - The demand that survival and hospitalisation for HF as primary endpoint is right. - The downgrading of symptomatic improvement as a possible primary endpoint is right. - The downgrading of improvement of exercise capacity as a possible primary endpoint is right.	Accepted.
4	It is recognized and highly appreciated that EMA has made to incorporate previous comments provided on the concept paper. The draft guideline as written provides an appropriate balance of directionality versus flexibility which should allow novel development approaches to be used in CHF, with the overall intent of facilitating access to valuable drug therapies. Indeed, HF studies are global and as such it is important to accommodate for regional differences in treatment practices. Not all systems or regional practices will admit similarly affected HF patients to hospital during a HF exacerbation; one factor that may contribute to these regional differences is the high economic cost of hospitalizations to health care systems.	Accepted.
6	HFA agrees with the general structure of the proposed CHMP Guideline on the clinical investigations of medicinal products for the treatment of cardiac failure. We welcome the opportunity to provide comments for consideration by the CVS WP for the final draft of the guideline. General Comment:	Not accepted. The guideline refers to the development of new therapeutic agents. The extension of indication of already approved drugs through a meta-analytic approach is outside the scope of this guideline and is covered by the following document: *Points to consider on an Application with 1) Meta-analyses 2) One pivotal study (CPMP/EWP/2330/99)*.

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	Some molecules like diuretics are used in heart failure and are now generic. They will never be tested in clinical trials. It would be worth giving the possibility to drugs with established clinical use and adequate scientific evidence to be approved using a meta-analytic approaches.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
70-82	6	Comment: HFA endorses the suggested update of the description of heart failure patients according to left ventricular function as this is in line with the recently released ESC/HFA guidelines on heart failure. HFA also welcomes the inclusion of patients hospitalised for heart failure or just discharged from hospital as a group of special interest.	Accepted.
71	4	Comment: An overlap in terms of pathophysiology, hemodynamics and neurohormonal abnormalities between HFrEF and HFpEF cannot always be completely ruled out. Proposed change (if any): "The distinction between patients with HFrEF from those with HFpEF is important because they represent groups with different ~~underlying pathophysiologic, haemodynamic and neurohormonal abnormalities, distinctly different~~ clinical characteristics, and dissimilar efficacy of existing therapies (2)."	Partly accepted. Section 6 reads: "*The cut-off of 50% for a diagnosis of HFpEF is arbitrary; patients with an LVEF between 40 and 49% are often classified as HFpEF in clinical trials*".
80	3	Comment: typo; delete "if" before "channel blockers"	Accepted. The typo has been corrected.
120-121	4	Comment: Improvement in functional capacity is an important endpoint from the patient perspective; as long as cardiovascular morbidity/mortality is appropriately characterized and shown to be either neutral or positive, improvement in functional capacity and/or symptoms should be adequate for registration in all symptomatic patients with heart failure.	Accepted (see section 4 and section 4.1.3). Section 4.1.3 has been revised. In selected patient populations with high unmet medical need (e.g. patients with end stage CHF, CHF with cachexia or hypertrophic cardiomyopathies and other specific

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Improvement in functional capacity may also be a relevant treatment goal in selected patients in symptomatic patients. The aims of treatment and assessment of endpoints are not different between patients with HFrEF and those with HFpEF.	etiologies), the effect of the treatment on exercise capacity may be considered as a primary endpoint.
124	6	Comment: HFA fully endorses the pursuit of improvement of functional capacity as a primary end point in selected patient populations.	Accepted. See above.
132-134	5	Comment: Event though the mortality is considered as a component of the main composite endpoint, should the study be powered to show a statistically significant result on the mortality?	Not accepted. This is not discussed in the guideline.
132-137	5	Comment: Why overall mortality is the preferred end point? If a drug is expected to decrease cardiovascular mortality and hospitalisation for heart failure thanks to its mechanism of action, but not playing a role on non CV mortality, taking all cause mortality as primary endpoint will lead to an increase of the number of patients to demonstrate statistical decrease of this endpoint. In conclusion, cardiovascular mortality, and not all-cause mortality, should be used as an endpoint for trials of new treatments for HF-REF, as reflected in the below mentioned article. "Falling Cardiovascular Mortality in Heart Failure With Reduced Ejection Fraction and Implications for Clinical Trials"	Not accepted. Please see sections: 4.1.1: "Assessment of mortality in confirmatory trials should include both all-cause mortality and cardiovascular mortality". and 5.1 of the Guideline: "*Even though cardiovascular death is an adequate clinical oucome to reflect the disease process targeted by treatments for heart failure, all-cause mortality may in many cases be the preferred choice*."

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		Rush CJ, Campbell RT, Jhund PS, Connolly EC, Preiss D, Gardner RS, Petrie MC, McMurray JJ JACC Heart Fail. 2015 Aug;3(8):603-14. Proposed change: Cardiovascular mortality is the preferred end point, alone or as a composite endpoint. All cause mortality should be a secondary end point and non CV mortality should be described.	
134	4	Comment: “Hospitalization for heart failure” is cited as a component of a composite primary endpoint. This term may, however, be too restrictive, given the increasing utilization of outpatient clinics to treat heart failure decompensation (see comment below). Outpatient HF events are increasingly being recognized as important events in the patients’ clinical course and should not be overlooked when capturing endpoint events. The widely-used term “worsening heart failure“ may be more appropriate to encompass all suevents. Therefore it is proposed that worsening of Heart Failure would be considered an over-arching term, and that it would include both hospitalisation for heart failure and outpatient worsening HF Proposed change: Accordingly we propose the following changes to the guideline: Replacement of “hospitalisation for heart failure” with “worsening of heart failure” particularly in line 134 and Line 138	Accepted. The comment is endorsed, changes had been made, please see sections 4.1.2 and 5.2.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Insert subtitle above line 139: “4.1.2.1: Hospitalisation for HF” and above line 150 “4.1.2.2 Outpatient worsening of heart failure”	
135-137	4	The current text implies multiplicity adjusted all-cause death is a preferred endpoint. We suggest the emphasis should be on cardiovascular (CV) death, not all cause death. All-cause death as a secondary endpoint sets a high bar for studies to achieve superiority as opposed to testing CV death and showing non-inferiority on non-cardiovascular death. For therapies specifically developed for the treatment of heart failure, effects on all-cause death are likely a result of a more prominent effect on CV death. We do not expect such therapies to meaningfully influence non-cardiovascular causes of death (such as death due to sepsis). The impact of non-cardiovascular death is also likely a function of the population sampled. For example, a study of an older population would be expected to have greater attenuation than one of a younger population due to a greater proportion of all-cause deaths being non-cardiovascular. This makes cross product comparisons more difficult.	Not accepted. Please see section 4.1.1 and 5.1.
138-153	4	We welcome the fact that the importance of worsening of heart failure in an outpatient setting is recognised and that the events may be captured as an endpoint. In the current era of heightened efforts to avoid or shorten hospitalization, episodes of clinical worsening of heart failure in chronic heart failure patients are being increasingly managed by short-term intravenous treatment or augmentation of oral therapy in the outpatient setting, such as emergency department visit	Accepted. The comment is endorsed an appropriate changes had been made (see section 4.1.2 and 5.2)

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		(without subsequent admission to the hospital), heart failure clinic, or community physician office, etc. In the PARADIGM-HF study of chronic heart failure patients with reduced ejection fraction, these non-hospitalised, outpatient episodes of worsening heart failure events were associated with a 4- to 6-fold greater risk of subsequent death in comparison with patients without these events, a risk similar to that following heart failure hospitalization (Okumura N, et al., Circulation 2016, 133: 2254-2262). Therefore, provided outpatient worsening heart failure events are rigorously defined and well documented, we propose that they could be considered for inclusion as part of a primary composite endpoint . Proposed change (line 152): The capture of events of WHF without hospitalisation may be warranted as ~~n additional endpoint~~ part of a composite primary endpoint, as long as rigorously defined and adjudicated. Further, we strongly urge that the concept of an Urgent HF Visit (e.g. emergency departments, observation units and other outpatient settings with urgent care capabilities) without subsequent hospitalization under the broader umbrella of “HF events” (including HF Hospitalization events and Urgent HF Visits as subcategories) is included in this guidance as a legitimate and acceptable endpoint for assessing efficacy of a drug in development. HF patients managed for HF exacerbations in the Emergency Department or through urgent non-scheduled outpatient visits have been shown to have similar baseline characteristics (Ezekowitz et	

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		al., Eur J Heart Fail 2008. 10:308–314). Moreover, management of HF patients in the Emergency Department or as an urgent non-scheduled outpatient visit portends similar risk for morbidity and mortality as management in the hospital setting (Skali et al., Eur J Heart Fail 2014. 16(5):560-5). Finally, treatment effects of contemporary therapies have shown similar results when looking at HF events including Emergency Department or urgent non-scheduled outpatient visits (Okomura N, et al., Circulation 2016.133:2254-2262). There is recent precedence for the expansion of the definition of HF hospitalization. In recent trials such as SHIFT and EMPHASIS, ER admissions for HF that extended over a calendar day were considered “HF hospitalization”. This precedence also extends to regulatory guidelines in another ICH region; the US trend of changing clinical practices has led to the publication "2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials" that proposes a HF endpoint event constructed independently of whether the HF exacerbation results in hospitalization. This report recognizes that exacerbation of HF can often be managed on an outpatient basis (Hicks et al., JACC 2015. 66(8):877-888) provided such HF events and its subcategories are well-defined, comparisons between investigational and prior therapies can still be performed.	
138-153	4	Comment: Under the assumption that HFH represent a very heterogeneous group of events, it might be worth considering	Partly accepted.

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		approach that also incorporate the length in hospital such as analyses of 'time out of hospital'	HFH group of events is discussed in section 5.2 and it is recommended to request a scientific advice due to methodological issues involved.
141-149	5	Comment: Recurrent hospitalization: the effect of confounding intervention including heart transplant and LVAD on the recurrent HFH end point can be overcome by the measurement of the number of days free from any terminal event and out of hospital, considering LVAD or heart transplant as a terminal event.	Accepted. This is now clearly stated (see section 5.2).
145-153	6	Comment: The adoption of recurrent event analyses is strongly supported.	Accepted (see previous comments).
150-153	5	Comment: Decrease in HF events is an important component of the benefit expected from HF drugs and has to be a component of the primary end point including Hospitalisation for heart failure and Urgent visit to emergency unit without 24 hours hospitalisation. For the same level of severity of symptoms and general condition of the patients, hospitalisation of the patient may differ according to hospital availability, incentive policy for avoiding hospitalisation, family and social context of the patient and is not per se a criteria of severity. Taking into account non hospitalised worsening in the primary end point, provided that all cases are adjudicated with well defined ciriteria could add 10-15% events (ref: Paradigm, Madit CRT) and decrease the time for completing a study .	Accepted. Worsening heart failure without hospitalisation is discussed in sections 4.1.2 and 5.2.
154-157	6	Comment: For events of worsening heart failure treated	Accepted.

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		outside the hospital settings adequate criteria for the definition of decompensation should be listed.	This is now discussed in sections 4.1.2 and 5.2.
155 - 160	4	Comment: Patients with cachexia or frail or elderly may be unable to undergo exercise testing and/or have HF-unrelated limitations to their exercise capacity. Consideration of exercise capacity as secondary outcome could be meaningful to quantify an objective correlate of the KCCQ physical limitations score or other PRO. Proposed change: "… the effect of the treatment on exercise capacity may be considered as a primary endpoint provided it is accompanied by an improvement in patient related outcome and that the cardiovascular safety profile is adequately characterised (see also 7.5 and 8.1). Alternatively, it may be considered as secondary endpoint that accompanies an improvement in patient related outcome (PRO) as primary endpoint."	Accepted. The comment is acknowledged and the text has been updated accordingly. Please see section 4.1.3.
157-158	5	Comment: The definition of unmet medical need can be extended beyond cachexia to pathologies without treatment including hypertrophic cardiomyopathies. Proposed change: an unmet medical need (e.g. [….] end stage CHF, CHF with cachexia, CHF associated with hypertrophic cardiomyopathies and other specific ethiologies).	Accepted. The text has now been revised, please see lines section 4.1.3.
157-160	4	Symptomatic improvement and improvement in functional capacity are very important to heart failure patients and an	Not accepted. The text has now been revised, please see section 4.1.3 and 4.1.4.

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		important goal of HF treatment. Prevention of deterioration of symptoms and functional capacity would also be considered viable goals of treatment. Therefore these endpoints should not be confined to “select patient populations with unmet medical need” provided that any effects on CV endpoints of morbidity/mortality are adequately defined and are not negative, the tools to assess symptomatic improvement are appropriately validated, and the changes are clinically meaningful. Proposed change (if any): In ~~selected patient~~ symptomatic patients populations with an unmet medical need (~~e.g. patients with cachexia or frail or elderly~~) the effect of the treatment on exercise capacity may be considered as a primary endpoint provided it is accompanied by an improvement in patient related outcome and that the cardiovascular safety profile is adequately characterised (see also 7.5 and 8.1).	
163-167	1	Comment: The use of PROs seems restricted: “PROs may include improvement of symptoms”, “PROs can be used as secondary outcomes” and “PROs should be considered as supportive”. Patient centered PROs like the CareQol deserve a dominant position in CHF studies Proposed change (if any): The CareQol CHF can be considered as primary outcomes next to other primary outcomes.	Not accepted. The use of PROs as primary end point is not endorsed, unless used in combination with functional capacity under exceptional circumstances.
164-168	5	Comment: It could be specified that if clinically relevant	Not accepted. The guideline does not discuss

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		improvement in well validated PRO is demonstrated, this will be recognised in the labelling.	reflection of PRO on the labelling.
167	4	Comment: As mentioned above, symptomatic improvement is highly relevant for patients in whom symptoms are not adequately controlled. The guideline at present does not support the use of a symptom endpoint as a primary measure of efficacy, on the other hand it is mentioned in 4.1.4 that PROs can be used as secondary endpoints. In 4.1.8 PROs are listed as part of the composite and hierarchically-ordered endpoints. Additionally, functional capacity can be part of a primary endpoint provided it is accompanied by improvement in PRO. Therefore, we propose that PRO could be included as primary end-points particularly if the same parameters suggested for functional capacity are met. Proposed change: Replace “PROs can be used as secondary endpoints in CHF studies and should be considered as supportive” with “appropriately validated measures of symptom burden may be used as primary or secondary endpoints in CHF studies, provided that the CV safety profile of the drug is adequately characterized and that there is no negative effect on mortality.”	Partly accepted. The whole paragraph on PROs has been re-written. Please see sections 4.1.4 and 5.4. The use of PROs as primary end point is not endorsed, unless used in combination with functional capacity under exceptional circumstances. Furthermore, it is now requested that scales or scores can be used for the assessment of symptoms provided that they are validated in the populations (and in the languages) in which they are being tested (see section 5.4).
167-170	4	Comment: It is stated that PROs may be used in support of the effect on exercise capacity for certain patient populations. This implies that functional capacity is a higher order endpoint than patient-related outcomes, which is questionable from a patient perspective. However, what is	Partly accepted. The text has now been revised, please see sections 4.1.3 and 4.1.4.

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		crucial is that any effects on functional endpoints and patient –related outcomes should be consistent directionally. Proposed change: Delete: "in patients with advanced disease and/or severe co-morbidities (end stage CHF, CHF with cachexia) where there is a need for palliative care, PRO may be relevant in support of the effect on exercise capacity" and add instead "Effects on an endpoint relating to symptom improvement should also be supported by directional consistency of accompanying improvements in the patient's condition, such as improvement in functional capacity."	
171-174	6	Comment: The use of PROs in heart failure patients in advanced disease or with severe comorbidities is strongly supported. However, advanced heart failure and cachexia need to be better defined or reference to relevant guidelines or consensus statements of expert societies should be made.	Accepted. A reference has now been added (see Ref 11).
177-183	4	Comment: In contrast to hemodynamic parameters, some of the mentioned biomarkers have actually been shown to correlate with outcomes and prognosis. The guidance might consider cross referencing to the ICH E4 guideline on Dose Response Information to Support Drug Registration mentioning that these endpoints could be considered for dose selection.	Partly accepted. Document "*Dose Response Information to Support Drug Registration (CPMP/ICH/378/95; ICH E4)*" is listed in Section 3 Legal basis and relevant guidelines. There are no biomarkers that have undergone a proper biomarker validation. Therefore, they cannot be used for phase 3 studies, in Phase 2 studies they can be used alongside the haemodynamic parameters that are needed to

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			elucidate the mechanism of action (see section 4.1.6).
181	4	Comment: Recognising the value of biomarkers, there may be instances where a sponsor would decide to run a study using biomarker as a primary endpoint. Whilst this may not be pivotal data, it may provide valuable scientific information supporting the B/R assessment of a new product Proposed change: To this end biomarkers cannot be included as primary endpoints in 180 phase III pivotal clinical trials in CHF	Accepted. Please see section 4.1.6.
184 -190	5	Comment: Please consider that the reduction in shocks can be the primary efficacy end-point of a study instead of mortality, for some treatments depending their mechanism of action.	Partly accepted. Please see section 4.1.7.
188	6	Comment: This is an extremely important new information as the majority of ICD are now implanted in patients with heart failure rather than in patients without heart failure. Past and recent clinical trials include only a minority of patients with ICDs/CRT-Ds.	Accepted. The comment is endorsed, please see section 4.1.7.
192-193	4	Comment: Wording in the current guideline could create confusion in its interpretation with regards to multiplicity. In order to avoid confusion we suggest breaking the sentence into below proposal. Proposed change: “Composite endpoints can be applied to CHF studies with the composite including mortality (overall or cardiovascular) and HFH. If a ranked endpoint is preferred	Accepted. The whole paragraph has been re-written. Please, see section 4.1.8.

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		mortality and HFH should be the first two hierarchical endpoints in the ranking procedure."	
192-196	4	Comment: We agree that mortality and HFH should be ordered first and second in a hierarchical endpoint, but suggest that the ranking of the subsequent endpoints shall not be specified in the guideline. Proposed Change: These endpoints may be followed in order of relevance by measures of functional status (6 Minute Walking 194 Test [6MWT], Maximum Oxygen Uptake [MVO2]), and PRO.	Accepted. See section 4.1.8.
198	3	Comment: "concomitant background medication" should be even broader to include palliative treatment (e.g. oxygen, transfusion, etc...)	Partly accepted. Concomitant background medication includes all medications needed according to the disease stage and co-morbidities. No changes to the text were considered necessary.
199 – 200	4	Comment: 'maintain stable background therapy throughout the study' should not exclude inevitable adjustments to diuretic doses or other dose adjustments typically required in heart failure patients during the conduct of a study when treatment duration may be over years. How do you reconcile with the explicit applicability of this guidance for 'patients with CHF including those in the post-acute phase of heart failure' (line 90), and with your guidance that 'patients hospitalised for heart failure (HFH) … can be included in studies to assess the effect of chronic therapies that are started during the hospitalisation, at discharge or during the	Partly accepted. The text has now been revised; please see beginning of section 5.

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		30 days after hospital discharge' (lines 297-299) Proposed change: Efficacy variables may be influenced by changes in concomitant background medications. Therefore, if possible, every effort should be made during the conduct of a study in patients with CHF to maintain stable background therapy throughout the study.	
203-205	4	Comment: One of the advantages of having all-cause death as primary endpoint is that it would make central adjudication needless. Proposed change (if any): "It is mandatory to report and adjudicate all mortality data in studies in CHF where survival is an endpoint of the study. Centrally adjudication is not necessary if all-cause death is the primary endpoint".	Not accepted. It is always important to have accurate information on cardiovascular mortality and this can be obtained only by central adjudication.
214-217	4	Comment: please slightly rephrase Proposed change (if any): HFH must be defined in the protocol by signs and symptoms of deteriorating clinical conditions along with signs of cardiac overload (e.g increased plasma levels of natriuretic peptides) as appropriate and the need for acute treatments for CHF (e.g., increase in diuretic dose, intravenous diuretics, or intravenous vasodilators/inotropes).	Accepted. The paragraph has been revised and includes the proposed suggestion. See section 5.2
222-223	4	Comment: We agree that the reasons for a change in background therapy should always be carefully recorded and that general recommendations should be provided in the protocol on the circumstances under which medication can be	Partly accepted. The text has now been revised, please see section 5.

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		adjusted. However, in an area such as heart failure where adjustments of multiple medications may be required frequently to manage the patient's clinical condition, investigators must be allowed discretion to make the final decision on the need for adjustment of medication. It is not clear whether the current text would foresee this approach. Therefore for clarity it is proposed make the following change: Proposed change: replace "and the criteria for these events must be pre-specified…. " with "and the protocol should include guidance on the circumstances under which background therapy may be altered"	
231-232	3	Comment: duplicated (same text as lines 237-238) Proposed change (if any): delete lines 231-232	Accepted. The text has now been revised.
237-238	4	Comment: repetition of lines 231, 232 Proposed change (if any): delete 237 and 238	Accepted. The text has now been revised.
239-240	4	The text states "in order to define an episode of de-compensation in the outpatient settings it is required to demonstrate a cardiac cause for the worsening of symptoms using the same definitions as for HFH". Whilst we agree with the principle outlined, we believe that the meaning of the text may be further clarified as follows: Proposed change: replace sentence above with "An episode of de-compensation in the outpatient setting should be	Accepted. The text has now been revised, please see section 5.2.

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		consistent with a cardiac cause for the worsening of symptoms, and the same definitions of HF symptoms and signs should be used in the outpatient setting as those used for HFH."	
242-245	4	When considering methods to assess functional capacity, it is suggested to add use of activity monitors to assess daily activities. This represents an alternative potentially important assessment technique which is likely to become a future gold standard, acknowledging that further study is required to validate any such methods. Proposed change: Add sentence "The use of activity monitors to assess daily activities may be considered, provided appropriately validated."	Not accepted. Activity monitors are not adequate to provide standardised measure of maximal functional capacity.
245	4	Comment: proposal to add accelerometry as useful functional test in a frail population Proposed change : such as stair climb test, accelerometry,...	Not accepted. See section 5.3.
248	4	Comment: proposal to add the term "premature" Proposed change (if any): the reasons for premature termination of the tests	Not accepted. The text has now been revised see section 5.3. The reason(s) for any termination of sub-maximal exercise tests should be specified a priori.
287-288	4	Comment: The proposed text as written elicits the question "what is a relevant number of patients?" and stipulating a	Accepted.

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		proportion or absolute number of patients will not improve the quality of clinical data or accelerate the provision of new treatment options for heart failure patients. While protocols frequently allow the inclusion of patients over 75 years of age, physicians are often hesitant to enroll such very elderly patients in clinical trials. Recommended change: "Appropriate efforts should be made to include A relevant number of patients over 75 years of age must be included."	It is now mentioned that an adequate number of very-old patients should be included in clinical trials (see section 6).
289	3	Comment: typo; add "be" before "differentiated"	Accepted.
290	4	Comment: One of the cut-offs needs to include EF 40%. We suggest that a reference is made to the ESC guideline (http://eurheartj.oxfordjournals.org/content/ehj/early/2016/06/08/eurheartj.ehw128.full.pdf) Proposed change (if any): "…those with reduced (LVEF ≤ 40%)…"	Accepted. Section 6 was revised.
295-299	4	Comment: This definition of patients hospitalized for heart failure is not universal and can be controversial. It is not clear to us why would it be necessary to be off parenteral treatments. Depending on the mode of action, we think that some chronic therapies could be started in patients after an acute decompensation still receiving parenteral treatments such as diuretics, independent on the fact whether the patient is in the hospital or not. The guideline should be flexible in this aspect.	Not accepted. In patients included in this guideline treatments should be started when patients are not receiving intravenous drugs (see section 6).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): “Depending on the nature of the claim sought and of the pharmacology of the investigational drug, patients hospitalised because of an acute episode of de-compensation heart failure who remain hospitalised can be included in studies to assess the effect of chronic therapies that are started during hospitalisation, at discharge or during the 30 days after hospital discharge.”	
300-301	4	Comment: Most CHF trials conducted so far distinguish between ischemic and non-ischemic etiology. Since in most cases of HF the underlying cause are multiple we believe it would not be accurately defined and may be challenging to define the “one cause”. Proposed change: “The pathophysiology of CHF studied should be defined in terms of aetiology as much as possible (i.e. top-down approach, e.g. ischaemic, non- ischaemic; if non-ischemic further definition if possible) .”	Partly accepted. See section 6.
303-305	4	Comment: To avoid misinterpretation of “standard of care in sizable number of patients” it is better to leverage guidelines and align with “guideline recommended therapy”. Furthermore, heart failure epidemiology and treatment practices are heterogeneous even within Europe. Proposed change: “Given the worldwide variability in therapeutic practices a sizeable number of patients included in clinical trials should be representative for the European population with regards to their ~~background treatment and standard of care~~ guideline recommended therapy.”	Partly accepted. The reference to the ESC clinical practice Guideline is included in this sentence in section 6.

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304-305	6	Comment: It would be helpful to provide regulatory guidance on the conduct of clinical trials in distinct subsets of chronic HF patients other than those simply identifiable from the left ventricular function. For example, genetically determined subpopulations, specific cardiac metabolic phenotypes (e.g. diabetic cardiomyopathy), ischaemic cardiomyopathy, druginduced (mostly anti-cancer) heart failure.	Partly accepted. It is now stated that a new therapy can be approved for subsets of patients with heart failure see section 6. This will largely depend on the indication claimed.
307	4	Comment: subgroup of interest to add Proposed change (if any): other patient characteristics (e.g right ventricular dysfunction)	Not accepted.
311-313	4	Comment: Guideline states “For studies to be conducted in patients with CHF, a period of stability of CHF medications is required before inclusion. In patients with CHF, uptitration of first line therapies should be conducted according to current clinical practice guidelines.” However, depending on the trial design it might be difficult to achieve a period of stability of CHF medication before inclusion in the trial. For trials including newly diagnosed patients (to target a first line therapy) or patients after a recent acute decompensation it might be unfeasible to require a period of stability. In addition it might be challenging to define stability (class of drugs, active ingredients, doses) In addition, this section contradicts statements in lines 295-299 regarding hospitalized and stabilized patients as they are likely to require further medication titration. Given that any	Accepted. The paragraphs have been re-written and the comments have been included. (please see also section 7)

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		potential impact of change in background medications should be negated through randomization, and that any changes in medication should be rigorously documented it is sufficient to state that patients should be on their optimal SoC aligned with guideline recommended therapy when enrolling into studies. Proposed change: For studies to be conducted in patients with CHF, a period of stability of CHF medications ~~is required~~ is preferable before inclusion. In patients with CHF, uptitration of first line therapies should be conducted according to current clinical practice guidelines.	
311-313	5	Comment: When the new treatment is started during hospitalisation for heart failure, the background treatment may not be stable. It should be specified that in this setting, optimisation of the background treatment should be made during a short period6-8 weeks after discharge.	Partly accepted. It was specified that the efforts should be put in place in order to uptitrate first line therapies according to current clinical practice guidelines.
315-319	4	The draft guideline as written requires that pharmacodynamics parameters to be tested include the effect of the agent on certain haemodynamic parameters. However, given the lack of predictability of stroke volume and PCWP for outcomes, it is suggested that these should be required only when there is a clear rationale to do so based upon mechanism of action or intended use. Proposed change: delete “the effect of the agent on haemodynamic parameters (e.g. stroke volume, pulmonary	Not accepted. These end points are required only in phase 2 studies (see section 7.1).

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		capillary wedge pressure)". Add as a new sentence "Evaluation of the effect of the agent on haemodynamic parameters (e.g. stroke volume, pulmonary capillary wedge pressure) may be considered based upon the mechanism of action"	
316	3	Comment: Clarify what "duration of action" means. Consider to also add "assessment of the magnitude of effect".	Accepted. Text has been revised.
320-321	4	Comment: This depends on the attributes of the therapy under investigation and the target patient populations. Recommended change: "Patients with degrees of CHF ranging from mild to severe ~~need to~~ should be studied, depending on the indication claimed."	Accepted. Text has been revised (see section 7.1).
334	3	Comment: Suggest to change last sentence to "Therefore, depending on PK additional data can be requested"	Accepted. Text was revised.
340	3	Comment: typo; add "dose" before "range"	Accepted.
340	3	Comment: Add "characterisation of the" before "dose concentration-response relationship"	Not accepted. Current text was preferred.
342-344	4	Comment: A study is not "powered" to assess a particular dose or treatment response. The word "sized" should be used. Recommended change: "Before starting a pivotal trial, the optimal/appropriate clinical dose(s) to be used must be identified by adequately ~~powered~~ sized and carefully designed dose-response study(ies)."	Partly accepted. Text has been revised.
346-348	4	Comment: It is recommended that the statement below is removed since it may seem to make assumptions including	Accepted. The whole paragraph has been re-written.

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		knowing the half-life, accumulation characteristics and PD response. Moreover, dose selection varies for therapies with different routes of administration and to selects "3 dosages" is arbitrary. Proposed change (removal of the sentence): "~~Dose-response studies should be randomised, placebo-controlled and double-blinded often using at least 3 dosages with a total therapy phase of at least 12 weeks to establish the clinically useful dose-range as well as the optimal dose~~."	
347	3	Comment: It should be more clear that the objective of the dose-response study should be to characterise the dose-response relationship, and that appropriate methods should be used to achieve this objective. Pair-wise comparisons (i.e. statistical test between each arm and placebo) are sub-optimal and better methods are available. Please refer to EMA/238961/2012	Partly accepted. The whole paragraph has now been re-written.
351-352	4	Comment: The text indicates that exploratory therapeutic studies should assess ….well-validated non-invasive haemodynamic responses" . However, as the guideline acknowledges, the endpoints in such studies should be tailored according to the product in question, considering both the mechanism of action of the agent under evaluation and it's intended use. What is intended by "well-validated haemodynamic responses" is unclear, hence it is also unclear as to whether a mandatory requirement for conduct would be appropriate for all products with differing mechanism of action.	Accepted. The text has been updated. See section 7.4.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: replace sentence “The endpoints in dose-ranging studies should be tailored according to the medicinal product in question and such studies should assess clinical symptoms as well as well validated non-invasive haemodynamic responses” with “The endpoints in dose-ranging studies should be tailored according to the medicinal product in question. Such studies should assess clinical symptoms and evaluation of other measures including neurohormonal response, functional capacity, echocardiographic parameters and renal function should be considered depending on the mechanism of action”	
352	3	Comment: Add that attempts should be made to also characterise the dose-(concentration)-response relationship for any emerging safety signals to guide dose selection.	Not accepted. This was considered outside the scope of this document.
357	5	Comment: Would embedding adaptive design within a single clinical trial be admissible (adaptive Ph III trial or seamless Ph II-III) – provided it is soundly based, well designed and discussed beforehand at a Scientific Advice?	Not accepted. This point is not covered by current document. As stated a scientific advice would be advisable.
358-360	5	Comment: A single pivotal study may be sufficient to confirm the efficacy of a new drug – provided the results are unequivocal. What is required to be considered as unequivocal: a high significant level with a p-value less than 0.01 ?	Not accepted. This is out of scope of the current Guideline. For general requirements regarding one pivotal trial please, see EMA Points to consider on an Application with 1) Meta-analyses 2) One pivotal study (CPMP/EWP/2330/99).

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			As per this guideline a single pivotal study may be sufficient to confirm efficacy of a new drug providing that the study is soundly based and well designed, executed, reported and the results are robust, clinically relevant, should be internally consistent and be externally valid. There is no sound scientific basis to give a pre-specified value for a p.
362-366	6	Comment: Although one single clinical trial can be considered adequate to warrant marketing authorization in certain cases, it will be important to state that the external validity of the study population will also be taken into consideration.	Partly accepted. Please, see above. For general requirements regarding one pivotal trial please, see EMA Points to consider on an Application with 1) Meta-analyses 2) One pivotal study (CPMP/EWP/2330/99).
388	3	Comment: Add “characterised and” before “documented”	Accepted.
393-396	4	Comment: “Such data could arise either from several trials or alternatively within the pivotal study by the use of all-cause mortality with a well-defined and acceptable non-inferiority margin. Interim analyses of pooled trial data can be acceptable to rule out an excess risk at initial submission.” The current text seems to specify that such data would only be available with formal testing for non-inferiority. It should be equally relevant if all-cause mortality is tested as a pre-specified endpoint.	The paragraph has been re-written, please see the new text.

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406-407	4	Comment: “Special emphasis should be put on renal function and electrolyte homeostasis.” Suggestion to strike the first sentence as these are not uniformly used studies nor have they been rigorously validated for use in clinical trials. Recommended change: ~~“Effect of alterations in regional blood flow in other organ systems, especially the kidney, heart and brain, may be studied~~	Not accepted. Please see sections 7.4-7.6 and 8.3.