European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON THE CLINICAL INVESTIGATIONS OF MEDICINAL PRODUCTS FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

Interested party (Organisations or individuals) that commented on the draft Guideline as released for consultation

Stakeholder No.	Name of Organisation or individual
1	ESC: European Society of Cardiology
2	ERS: European Respiratory Society
3	IFAPP: International Federation of Associations of Pharmaceutical Physicians
4	EFPIA
5	ACTELION Pharmaceutical Ltd.
6	Prof Kleber

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1. GENERAL COMMENTS – OVERVIEW:

Stakeholder No. *(see coverpage)*	**General Comment (if any)**	**Outcome (if applicable)**
1	These comments were brought together by the ERS working group on pulmonary circulation, in collaboration with the working group on pulmonary circulation of the European Society of Cardiology. The pulmonary hypertension working group of the European Respiratory Society welcomes the EMEA's initiative to implement guidelines for endpoints to be used in future clinical trials. The members of the working group also agree to most parts of the content of the draft version. They appreciate the opportunity to provide comments.	
2		
3	The guideline is well written and updated to most recent scientific evidence. We identified only 2 minor points which we feel it may be appropriate to better specify in the text.	
4	This draft guideline is well written and balanced and provides useful guidance for the development of drugs for the treatment of PAH, even though it is mainly focused to a restricted number of conditions listed in the clinical classification reference (group 1, subgroups 4.1 and 4.2). Please find below some comments with proposed changes and some questions for clarification.	
5	This draft guideline is overall well written and balanced and would provide useful guidance for the development of drugs for the treatment of PAH.	
6	Prof Kleber consents with the draft guideline.	

2. SPECIFIC COMMENTS ON TEXT

Stakeholders 1 and 2: ESC and ERS

Line No of the first line(s) affected	Comment and Rationale; proposed changes	Outcome
Title and content	The guidelines focus on pulmonary arterial hypertension (PAH). As trials are now being conducted also in other forms of pulmonary hypertension (PH), specifically in chronic thromboembolic PH (CTEPH) and in PH associated with chronic lung disease, we suggest adding a statement that these guidelines may also apply to trials in other forms of PH.	Partially accepted. The guideline's scope is PAH. It can apply to CTEPH based on clinical experience showing that specialized PAH-therapy can be beneficial in some cases. However, PH due to lung diseases is a different pathological/clinical category and falls outside the scope of this guideline.
5	The hemodynamic definition of PH has been revised during the 4th World Symposium on Pulmonary Hypertension which was held 2008 in Dana Point, California. The revised European Society of Cardiology (ESC) and European Respiratory Society (ERS) PH guidelines to be published in September 09 concurrently on the European Heart Journal and on the European Respiratory Journal have adopted this new definition (Mean PA pressure ≥ 25 mmHg at rest; the exercise criterion has been abandoned). **Proposed change (if any):** We suggest that this new definition is incorporated into the EMEA guidelines.	Accepted.
9	In a same line of argument we suggest that the EMEA also adopts the revised classification from Dana Point which will also be used in the new ESC-ERS PH guidelines to be published on September 09 concurrently in the European Heart Journal and in the European Respiratory journal.	Accepted.
74	Treatment of PAH has two major objectives: (i) improvement in exercise capacity, i.e. improvement of symptoms, and (ii) prolongation of the time to clinical worsening, and ultimately, of the time to death. In mildly symptomatic patients with earlier disease stages, improvement in exercise capacity may be less important than slowing disease progression. In contrast, in severely impaired patients with advanced disease, improving exercise tolerance may be the primary goal. There is no single endpoint that addresses both goals. We agree with the CHMP proposal to keep either 6 min walk test or time to clinical worsening as preferred primary	Deterioration in the 6-MWD is a proposed component of TTCW and it is expected that investigators will readily incorporate the 6-MWT in the definition of TTCW

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	endpoints. We also suggest that trials focusing on time to clinical worsening should utilize 6 min walk testing as a secondary endpoint, and vice versa.	
121	We agree with the EMEA that the 6 min walk test remains a valid tool to assess improvement in exercise capacity and we believe that the 6 min walk test should remain an endpoint, either primary or secondary, in PAH trials. The EMEA suggests also that "the minimal meaningful clinical difference needs to be defined *a priori* based on scientific evidence". However this may be difficult because if the clinical relevance may be defined for *an individual patient* (for example > 30 to 50 m) it is more complex to identify the clinical relevance for the *average value* observed in a clinical trial. The clinical relevance of a trial which primary end-point is the 6 min walk should be based not only on the absolute value of the average increase of this parameter but also on the concomitant favourable results of reinforcing secondary end-points such as clinical worsening and hemodynamics (for example reduction in pulmonary vascular resistance). The above issue is even more relevant in conditions in which the 6 min walk test may be less useful as in trials on PAH patients already treated with approved drugs (combination studies) or in other forms of PH, and the field should remain open for other concomitant measurements.	Accepted.
126	We also agree with the EMEA that time to clinical worsening will be an important primary or secondary endpoint in future PAH/PH trials and that a generally accepted definition is desirable. The EMEA proposal is in line with a recent proposal from the 4th World Symposium on Pulmonary Hypertension. There is however the need for clarification with some criteria: 1. All-cause mortality is certainly and important an undisputable endpoint 2. Your definition of PAH unplanned hospitalization (4.1.2) is appropriate especially if it is adjudicated/confirmed by a blinded committee. 3. It would be helpful to clarify that worsening in functional class is a sufficient but not a necessary criterion for clinical worsening. The criterion of a decline in 6 min walk distance > 15% from baseline on at least 2 consecutive measurements should be sufficient as it indicates clinical deterioration. In other words, it should be clarified that the point 3 in the	Accepted.

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	paragraph 4.2.2 should be considered fulfilled if only one of the three listed components is fulfilled. In addition a blinded adjudication committee should validate also this component defined as time to PAH-related clinical deterioration.	
166	Regarding 5.1. We believe that it is no longer justified to approve PAH drugs for definite functional classes. Although we agree that the evidence is strongest for patients in functional class III, there is also substantial evidence for most drugs in functional class II. Patients in functional class IV were a minority in most PAH trials. This has led to the paradoxical situation that in some European countries, no drug has been approved for patients in functional class IV. In our opinion, drugs should be approved for a disease or a condition but not for functional classes as the distinction between these classes is arbitrary and subjective.	Not accepted. The severity of PAH is still classified according to NYHA/WHO, with evidence of benefit mainly shown for patients in FC II- IV. The benefit/risk of each specialized PAH-therapy should be individually investigated in each disease severity to allow adequate conclusions. For example, the benefit/risk of epoprostenol is not expected to be positive for FC II and that should be specifically mentioned in the indication.
203	In paragraph 6.2 you suggest that in exploratory phase 2 studies, a placebo control arm could be permitted in naive patients. Based on a recent metaanalysis showing improvement on survival and reduction of hospitalizations (1) with the approved PAH drugs we suggest that also in phase 2 studies it is not ethical to include naive patients (at least in countries in which PAH approved drugs are available). Obviously, also in phase 3 confirmatory studies included patients should be treated with at least one PAH approved drug (for at least 3 months) before being randomised to placebo or the experimental compound.	The argument is accepted, but it is already mentioned that these studies “could” be performed with the possibility of an ethical issue arising.
215	In the paragraph 6.3 you suggest to utilise in confirmatory phase 3 studies an active control group with an approved PAH medication defining the non-inferiority margin. We respectfully believe that the sample size required by non-inferiority studies would be difficult to be achieved in a rare condition such as PAH. Including patients already treated with at least one approved PAH drug we can still utilise placebo as control for the investigational compound avoiding ethical concerns and utilising the superiority design.	Not accepted. The argument is acknowledged, but an add-on study design will result in an “add-on” indication. For applicants seeking a monotherapy indication, the option is obviously limited to a non-inferiority design.
	We definitely agree with the need to implement a document addressing the	A separate addendum addresses PAH in

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	problems of the approval of PAH specific medications in paediatric PAH subjects. PAH in this setting is even rarer than in adults and the possibility to achieve adequate sample sizes is reduced. In addition, the heterogeneity of the subjects in the age range between 0 to 18 years (or even up to 12 years) makes very complex the identification of appropriate end-points. From the ethical and practical point of view, it is difficult to convince the parents to accept a placebo-controlled study for their children once a medication has been shown to be effective in the adults. The only RCT completed in the pediatric PAH population (as compared to 26 RCTs in adults) has taken more than five years to be completed and has required the inclusion of many centers in countries without PAH drugs availability. For all these reasons, our suggestion would be to perform a 3 to 6 months pharmacokinetic (plasma levels according to different doses/Kg) and pharmacodynamic uncontrolled study (haemodynamics + 6 min walk test if more than 6-8 years) for medications approved in adults. The sample size should be not more than 50 -80 patients. The objective should be to confirm the same directional favourable changes observed in adults, to establish if dose adjustment is required and to confirm safety.	pediatrics that is currently under discussion.

Stake holder 3: IFAPP

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164	We believe it is important to add the importance to collect patients feelings using a patient diary card. Many times patients do not report the ability/inability to perform daily activities, which may have a significant impact on their QoL. **Proposed change (if any):** At the end of line 164 add a paragraph with the recommendation to collect daily information with a patients diary card.	Partially accepted. No need to mention a patient card separately, as this is included under 4.3.2: Health-Related Quality of Life Measures

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232	We believe it is important to include the opportunity to use adaptative design. Considering the rarity of patients, sponsors should be encouraged to use this design in a multiple dose Phase II design, moving then into a Phase III with the best selected dose. **Proposed change (if any):** At the end of line 195 add a paragraph stimulating the use of adaptative designs, especially suggesting to combine Phase II and III.	Partially accepted. Though adaptive design may be relevant for PAH trials, no need is seen to explicitly mention these designs as they are still under discussion in the CHMP. In section 6.3, the concept of other study designs is not excluded. In section 4, applicants are advised to seek protocol assistance when designing their studies. These references are considered sufficient.

Stake holder 4: EFPIA

Line No of the first line(s) affected	Comment and Rationale; proposed changes	Outcome
Line 9, par 1	Table 1: Clinical Classification of Pulmonary Hypertension. The 2003 World Symposium on PAH, Venice 2003. This classification as well as the definition of pulmonary hypertension has been slightly revised at the World Conference on PH in Dana Point in 2008. **Proposed change (if any):** Include the revised Dana Point classification and definition of pulmonary hypertension, which reflects current state-of-the-art.	Accepted.
Line 22, par 9	The scope is limited to PAH. In the Dana Point 2008 guidelines the use of PAH drugs in other forms of PH is recommended under certain circumstances. There is a significant unmet need and guidance on drug development in these other segments would be helpful. **Proposed change (if any):** Consider expansion of the clinical development guidance to include other forms of pulmonary hypertension	Partially accepted. The need to address other forms of PH is acknowledged but the scope of this guideline is PAH. The guideline may also apply to CTEPH. For the applicability to other groups, scientific advice from the SAWP is recommended.

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47	"Survival has been extensively studied in idiopathic pulmonary arterial hypertension." **Proposed change (if any):** Term "extensively" looks overstating the current knowledge. We propose also to include experience regarding survival from European registries, e.g., Humbert, Am J Resp Crit Care Med 2006	Accepted.
2. Scope, lines 56-60	The scope of the guideline is confined to subgroups 1, 4.1 and 4.2. Additional guideline/note for guidance might be needed to complete coverage of all conditions associated with PAH. In case of treatment of subgroups 4.1 and 4.2, cross-reference to existing or to be implemented guidelines for treatment of pulmonary thrombo-embolism should be made. **Proposed change (if any):** Add references to guidelines for other forms of PAH not included in the present GL	See before.
64, 65	Note for guidance on Clinical investigation of medicinal products for the treatment of cardiac failure CPMP/EWP/235/95, Rev. 1. addresses a different target population with a different pathophysiology. **Proposed change (if any):** We propose to delete the reference to this guideline.	Not accepted. Many similarities exit between both conditions, making the reference still relevant.
4.1.3 Clinical symptoms, lines 102-107	Clear rules for using symptoms as primary or part of a composite endpoint should be given. If they cannot be used as primary or as a co-primary (not as part of a composite endpoint), it should be clearly stated as such. E.g. what if 6-MWT is chosen as the primary endpoint? **Proposed change (if any):** Delete primary; propose to clarify that FC should be a component of the composite TTCW endpoint.	Accepted. The text has been re-edited.

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	It should be made clear that this refers to Time to Clinical Worsening, and it is not necessarily the primary endpoint. Define role of symptoms as endpoints	
Line 105	A long-term improvement endpoint is one described as measured for "not less than 6 months". **Proposed change (if any):** Suggest not limiting endpoint to "not less than 6 months". Data at shorter durations may also be helpful (3 – 6 months). Also need to give consideration to the utility of placebo controlled study designs in this regard.	Accepted.
109-110	Shouldn´t it be: "has been" instead of "was" to highlight that 6MWT will continue to be a valid primary endpoint. And why mentioning short-term improvement? **Proposed change (if any):** We propose to replace "was" by "has been". We propose to delete "short-term" as this is not clearly defined what is meant with short-term.	The first change is accepted. The second change is not accepted, as three months is considered a short term.
112	"when the proposed indication is restricted to …" implies that this is not sufficient or recommended and has a negative connotation. **Proposed change (if any):** We propose to delete "restricted to".	Not accepted. The 6-MWT is not the encouraged primary endpoint to be used in this fatal disease.
Line 113	Data does exist to indicate that there is a relationship between changes in 6MWD and survival. There is no data to suggest this for clinical worsening endpoints. **Proposed change (if any):** Propose new text: "such an approach has its limitations considering the relatively small amount of data currently available showing correlation between improvement in 6MWT and improvement in survival"	Not accepted. The current text is considered adequate.

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Line 114	Decrease of 15% in 6MWT – is this applicable for all disease severities? The decrease by 15% rule seems to be suggested as a "success" criterion for 6-MWD in itself. This is a measurement on a continuous scale, and should not be dichotomised. Reference to acknowledged/accepted minimal clinically important differences (MCID) for 6MWT should be given **Proposed change (if any):** Reduction in 6MWT should be objective and 15% on two separate measurements is an example, but the applicant may offer alternative definitions dependent on patient population being studied etc. 6MWT is clearly still a valid endpoint It should be made clear that this rule relates to deterioration in 6-MWT if used as a component in Time to Clinical Worsening. The primary analysis for 6-MWT should remain mean or median change from baseline.	Not accepted. The current text is considered adequate as the values are only given as a guidance. It is also now emphasized that the clinical relevance of the 6-MWT should be seen in light of the results of the investigated secondary endpoints. The text is clear that the improvement in 6-MWT can still be used as the primary endpoint, while deterioration in 6-MWT can be used as a component of TTCW.
4.2.1 Improvement in Exercise Capacity, lines 123-125	It is not clear why the concept of clinical impact is given to be anticipated for non-idiopathic PAH, less severe PAH patients or in combination therapy. This should be taken as a general concept (see 4.1.4) " provided there are no negative safety signals". This is confusing as adverse reactions are seen with all drugs; whether these are regarded as negative safety signals or not may not be assessable. **Proposed change (if any):** We propose to put in "positive benefit-risk ratio or assessment" instead	Accepted. The section has been revised.
Line 126	Time to Clinical Worsening Criteria **Proposed change (if any):** Variety of different definitions being applied by KOL's both in EU and globally which makes conduct of global clinical trials particularly challenging. Consensus is needed within the community and Agencies	Partially accepted. The need for consensus is acknowledged but is not practical at the time being.

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133-134	The list of components for a TTCW endpoint is quite limited. We propose to amend this list. It would be helpful if more information was given on the degree of deterioration of exercise capacity that would constitute clinical worsening. **Proposed change (if any):** We propose to add at least: stagnation in functional class, need for lung transplantation, need for treatment escalation (adding further PAH specific drugs).	Partially accepted. The guideline proposes some components of the endpoint which are thought to be less subjective than the others. In case an applicant proposes another definition, this has to be adequately justified.
Line 136	In section 4.2.2 it states that any chosen parameter should not only be clinically relevant but also well validated. It then goes on to say that the composite endpoint should be tailored with respect to the severity of the target population. **Proposed change (if any):** Propose the individual components are validated and not the composite.	Partially accepted. The text is clear that every parameter should be separately validated.
136-137	"centrally adjudicated" may be a high hurdle and does not necessarily lead to better assessment. It increases complexity and costs and might interfere with the individual investigator' s assessment. **Proposed change (if any):** Recommend blinded assessment of relevant endpoints at the respective center itself. Reference with some useful recommendations: Dechartres, J Clin Epidemiol 2009	Not accepted. The studies in PAH are usually world-wide, a need for central adjudication is accordingly considered necessary.
4.2.2 Time to Clinical Worsening, lines 139-140	Claims to be substantiated from the data are a general rule. **Proposed change (if any):** Delete the sentence**.**	Not accepted. This sentence emphasizes that general claims are not encouraged.
140-142	Individual components of Time to Clinical Worsening may be of very low incidence and therefore should be considered separate secondary efficacy variables in themselves. But individual components should be summarised descriptively, but should not be subject to formal statistical testing.	Partially accepted. It is important to describe the contribution of each component of the endpoint to the results. This is essential to assess the clinical relevance of the results. This does not preclude investigating other secondary endpoints

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	Proposed change (if any): Remove the reference to secondary endpoints. Individual components should be summarised descriptively, but should not be subject to formal statistical testing.	as well.
146-147	The relevance of heamodynamic data has not been made clear adequately. See Expert recommendation from the ESC 2008. Several recent publications highlight the importance of haemodynamics as prognostic factors and correlate decrease in PVR with significant improvement in survival, in particular in CTEPH. (JAAC 2008, Jais et al.,Vol. 52, no. 25) **Proposed change (if any):** Haemodynamic data can be very useful, n particular in CTEPH. They are very useful also for phase II. Please update accordingly.	Partially accepted. The relevance of hemodynamic data in phase II studies in the dose finding phase is already highlighted in the draft guideline. However, their role in confirmatory studies is still secondary. The referenced article was not able to show the clinical relevance of the reduction in hemodynamics in CTEPH.
150	The draft guideline states "A more important role for haemodynamic measurements is expected in the paediatric investigation for PAH drugs." Since issues due re-catheterization in children have been encountered, this concept should be revised. Moreover, a relationship between magnitude of change in hemodynamic parameters and change in functional capacity has not been established. **Proposed change (if any):**	The reference to paediatric PAH is now deleted.
4.3.2 Health-Related QoL Measures, lines 156-159	Examples of accepted PAH-related tools/questionnaires for assessing QoL (e.g. Cambridge Pulmonary Hypertension outcome Review) should be given. **Proposed change (if any):**	Not accepted. This point has been raised before, and it was decided that mentioning the CAMPHOR QoL questionnaire is still pre-mature.
168, 169	Does this mean that patients need to be classified according to NYHA/WHO functional class at baseline? **Proposed change (if any):** It is our understanding that the CHMP encourages studies in functional class II	Partially accepted. Patients should be mainly stratified according to the NYHA/WHO classification at baseline. So far, any claims are based on this classification. No separate studies are needed for different functional classes. To

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	(mild), III (moderate) and IV (severe stage of disease). However, it is not clear whether these patients need to be investigated separately (different studies) or in a stratified manner (same study). Recommend to use consistent wording for NYHA/WHO functional class.	facilitate comparison with other studies, categorization according to the distance walked in the 6-MWT and based on hemodynamic is also encouraged.
171, 172	The use of stratification is unclear. It would be very difficult to stratify by every subgroup and combination of subgroups due to the rarity of the disease and the low patient numbers in each of those subgroups. **Proposed change (if any):** Please clarify in which circumstances stratification should be used, and when a simple subgroup analysis (without stratification) would be sufficient.	Accepted. Text is adapted.
177	Empirical use of calcium channel blockers should not be allowed. **Proposed change (if any):** Clarify, that these are not the PAH responders. Low dose ca -channel blockers should be allowed as concomitant treatment.	Not accepted. Empirical already signifies that these patients are not responders.
5.2 Background treatment, lines 179-182	Since development of drug as monotherapy or add-on may vary with patients' functional class, allowed background treatment for different patients population should be outlined. Moreover, a number of potential combination is high and the statistical approach will be problematic. What would be considered a sufficient number of patients on each class of background therapy?	Not accepted. This amount of detail is not needed.
221	Non-inferiority studies are suggested here. For standard studies, the non-inferiority margin might be chosen as one-half the expected effect size of the comparator, which would give a study size around twice that of a placebo-controlled superiority study. **Proposed change (if any):** Is there some flexibility in the choice of non-inferiority margin, so that studies of a practical size can be planned?	Scientific advice from the CHMP should be sought to address these issues. Section 4.

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234, 235	"Due to the rarity of this disease, the safety database may be too limited to allow for adequate safety analysis." What does this mean? Which number would be regarded to be sufficient? **Proposed change (if any):** We propose to change this to: "the safety database may be quite limited", and delete "to allow for adequate safety analysis"	Not accepted. This sentence has implications on the registration procedure. In some cases, the safety database is considered limited, and the drug is registered till more safety data is available through a SOB or FUM.
238	"it must be shown that the drug does not have adverse effects on morbidity or mortality" We seek clarification as to how this should be shown. **Proposed change (if any):** Please clarify	Not accepted. The sentence is clear and no explanation is needed on how to show that a drug has no deleterious effect.

Stake holder 5: ACTELION

Line No of the first line(s) affected	Comment and Rationale; proposed changes	Outcome
Lines 9-42	It is anticipated that the table will be amended to reflect the updated classification agreed at the Dana Point meeting in 2008.	Accepted.
Line 54	Since no clinical relevance has been attached to endothelin (type A and B) receptor selectivity an amendment is proposed: **Proposed change (if any):** …selective and non-selective endothelin **receptor** antagonists…	Not accepted. A distinction should be made as the clinical relevance is not yet known.
Lines 82-92	Actelion acknowledges the importance of providing data on (allcause) mortality in PAH therapeutic studies and that mortality is an important component of the primary	The arguments are acknowledged, but the text is considered adequate to convey the message.

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	endpoint in trials focusing on clinical worsening/disease progression in PAH. However, given that PAH remains a rare disorder, requiring that a new drug should be **shown** to have no detrimental effect on survival introduces a significant hurdle, which is also not fully defined in the current version. Controlled clinical trials can hardly be dimensioned to meet this requirement of **demonstration** and long-term, uncontrolled studies cannot provide **proof**. (*cf* also section 6.3) **Proposed change (if any):** The guideline should recommend that survival be followed in all studies and that patients should be followed at least for vital outcome until the end of study,irrespective of whether they continue on study drug or not. The wording should be changed to emphasize that for any new drug, there should be data on all-cause mortality to provide reassurance regarding the absence of a detrimental effect on survival.	
Lines 94-100	The section should acknowledge that the morbidity assessments need to be adapted to the disease severity of the population under study.	Accepted.
Lines 105-106	It is unclear why the CHMP would want to restrict its assessment on benefit for WHO/NYHA functional class only to effects lasting at least six months. WHO/NYHA functional class has been an accepted secondary endpoint in more short-term trials focusing on exercise tolerance. The CHMP should reconsider the proposed wording or provide rationale.	Accepted. The reference to an exact time point is deleted.
Lines 109-117	The second part of the paragraph (relating to deterioration of 6-MWT as a sign of clinical worsening) might fit better in section 4.2.2	Not accepted. This section describes the utility of 6-MWT as a whole (both improvement as a primary endpoint, or deterioration as part of TTCW).
Lines 127-142	Actelion supports the CHMP approach that clinical worsening must be a composite endpoint and that the definition of the components needs to take into account the characteristics of the targeted population. An overly prescriptive definition should, thus, be avoided. Nevertheless, account should be taken of recent expert consensus, as expressed in publications from the 2008 Dana Point meeting. Any attempts at harmonization of definitions with the FDA would also be supported.	Partially accepted. It is difficult to reach consensus regarding the definition of TTCW. The current definition is based on discussions with EU Experts. There is no FDA guideline to harmonize with.
Lines 167-	PAH is a progressive disease and without therapy patients will worsen and move	Not accepted. See before.

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173	through the NYHA/WHO functional classes. Rather than supporting a focus on a specific baseline functional class, there should be encouragement to, where possible, enrol a broad population of symptomatic PAH patients (across aetiologies), saying that the approvable therapeutic indication would take into account the consistency of findings across PAH aetiologies and baseline functional status. The requirement that studied patients should be adequately characterized at baseline is, of course, supported.	
Lines 175-182	The guideline should take into account that, given the rarity of PAH and the competition for patients to be enrolled in clinical trials, standardization of background therapy is not practically feasible and that stratification for different background treatment may not usually be possible. It should, rather, be acknowledged that conclusions on benefits for treatment combinations usually will have to be based on subgroup analyses that support consistency with the overall primary endpoint outcome.	Partially accepted. PAH trials are conducted world-wide; the results can be confounded by background medical interventions. This should be standardized “as much as possible”.
Lines 220-222	The proposal that for monotherapy, non-inferiority studies on exercise capacity can be performed is perhaps not realistic. Taking into account the variability of exercise tolerance testing and the constraints imposed by the rarity of PAH, it should, rather, be acknowledged that 3-arm studies of limited duration (3 months), including placebo and a reference ("benchmark") active therapy could be a way forward to provide the necessary documentation and proof.	Partially accepted. A non-inferiority trial is one example of claiming a monotherapy indication, though it is recognized it may be difficult. The draft guideline does not exclude other study designs, which should be better discussed and justified with the SA groups.
Lines 229-230	As discussed above, the statement that effects on mortality can be reported in "an open extension phase" is at odds with the requirement to **show** the absence of detrimental effects on survival.	
Lines 238-239	Please, refer to comments above regarding the requirements for **demonstration** that the drug does not have adverse effects on morbidity or mortality	