26 May 2015

Submission of comments on 'Draft qualification opinion of qualification of exacerbations of chronic pulmonary disease tool (EXACT), and EXACT-respiratory symptoms measure (E-RS) for evaluating treatment outcomes in clinical trials in chronic pulmonary disease’ - EMA/CHMP/SAWP/178465/2015

Comments from:

| Name of organisation or individual |
| --- |
| EFPIA – Sini Eskola (sini.eskola@efpia.eu) |

*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

1. General comments

| Stakeholder number*(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)*(To be completed by the Agency)* |
| --- | --- | --- |
|  | EFPIA welcomes the qualification opinion on the use of EXACT PRO and EXACT-RS as exploratory end points and recognises this as a significant step forward for both tools. Given that the qualification opinion was based on evidence available in late 2011/early 2012, EFPIA feels that more up-to-date evidence needs to be taken into consideration for the final opinion.EFPIA notes that a number of relevant studies have been conducted by its members, the results of which may address some of the limitations raised in the draft qualification opinion. In addition to these points, EFPIA feels that the qualitative work conducted to develop the EXACT-PRO is sufficient from a PRO development perspective to support full qualification, not just as an exploratory endpoint. Please refer to the two ISPOR manuscripts detailing appropriate PRO development processes. To this point, it would be helpful if there was a (voluntary) mechanism for incorporating information from these studies into the SAWP qualification process.It would also be helpful if the qualification opinion could clarify whether EXACT-PRO and E-RS would currently qualify for inclusion in the Summary of the Product Characteristics (SmPC), e.g. section 5.1. EXACT-PROEXACT-PRO has been developed for specific claims in a specific population, designed to match the characteristics of a typical COPD trial population. However, in some cases, the research community is using the instrument for different purposes than intended and in (largely) unselected patient populations. The SAWP’s view on generalizability of the instrument in the context of target population and intended use would be helpful (as the instrument is further validated).EXACT-PRO generates a wealth of additional data beyond that used in the current algorithm focused on calculating the number of EXACT-PRO events. In particular, inspection of the individual time courses show distinctly different patterns of response: some patients display wide day-to-day variability, others show a progressive worsening without defined discrete ‘events’ and only a minority of subjects show a stereotypical pattern where a discrete episode of clear worsening occurs that has a defined duration. These different patterns may indicate a fundamental distinction in clinical phenotypes. As currently used, the algorithms may obscure such patient subpopulations – to that point, EFPIA would welcome SAWP thinking on the use and clinical relevance of this data beyond the proposed algorithm definition of eventsThe dynamic response of the instrument has only been convincingly demonstrated to date in clinical studies of bronchodilators and not in studies of anti-inflammatory agents. For an instrument to be truly useful in characterizing COPD exacerbations, it should also show sensitivity to treatment with an anti-inflammatory agent. EFPIA would recommend the incorporation of data from completed studies not included in the initial submission to evaluate this.EFPIA acknowledges the decision to exclude physical activity from the final conceptual framework for both the EXACT-PRO and E-RS based on the performance of the relevant item during the item reduction process and agrees with the recommendation to utilise EXACT-PRO in parallel with measures for (daily) physical activity where appropriate in clinical development.EXACT-RSThe EXACT consortium recommends the use of pre-specified subscales to address this issue. EFPIA would welcome feedback on this aspect from SAWP with additional comment in the opinion.SummaryEFPIA therefore welcomes further clarification on what additional specific evaluation, data and analyses would be required for EXACT-PRO and EXACT-RS to be accepted for use as a primary or secondary efficacy endpoint.In order to properly address the points above, EFPIA recommends holding a workshop involving industry stakeholders, as well as the wider scientific community to discuss the use of the EXACT and E-RS tools further and to consider the wider evidence available (and further evidence needed) to support their use as primary and/or secondary efficacy endpoints in clinical trials. |  |

1. Specific comments on text

| Line number(s) of the relevant text*(e.g. Lines 20-23)* | Stakeholder number*(To be completed by the Agency)* | Comment and rationale; proposed changes*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome*(To be completed by the Agency)* |
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| 185-188 |  | EFPIA believes this section of the document is taken from the submission made by Evidera (formerly United Biosource Corporation).Comment:It may be preferable to provide context to the statement:“The E-RS is intended for use in the following target population: “The clinical diagnosis of COPD or chronic bronchitis that follows is prescriptive – essentially a list of inc/exc criteriaProposed change (if any):The E-RS *was validated in and is therefore* intended for use in the following target population: It would be helpful to clarify if the EMA/CHMP intends to restrict claims from the derived use of E-RS to the COPD and chronic bronchitis patient population described in lines 185-188. |  |
| 194-196 |  | Comment:The statement: “generally 12 weeks in duration” was noted, presumably extracted from EXACT user documentsInclusion of this text suggests that the EMA/CHMP might consider 12 week studies in COPD drug adequate as the basis of approval for anti-microbial therapies of ABECB-COPD with FEV1 and/or symptoms as major endpoints.Proposed change (if any):It would be useful to provide clarification on this point with respect to the duration of the efficacy studies in line with the available COPD CHMP guideline. |  |
| 200 |  | Comment:“... E-RS scores may serve as primary, co-primary, secondary, or exploratory endpoints in clinical trials…”The statement, from the written submission , may be misinterpreted as endorsement of E-RS scores as a primary endpoint in phase III clinical trials by EMA, when this is not reflected in the draft qualification opinionProposed change (if any):E-RS scores *have been proposed to serve* as primary, co-primary, secondary, or exploratory endpoints in clinical trials… |  |
| 127; 204; 212 |  | Comment:The involvement of the FDA is mentioned several times in the draft qualification opinion. The EMA draft opinion is more advanced than the FDA position on EXACT-PRO; furthermore, the FDA has not provided any feedback on the EXACT-RS submission to date.EFPIA also understands that the SAWP/CHMP draft qualification opinion may have been delayed due to the protracted nature of the similar FDA process.It would be helpful if there was greater transparency around the interaction with the FDA (and other global agencies) with further information provided in the qualification opinion. This may facilitate a more regionally and temporally-aligned approach to qualifying the use of novel PRO instruments (or other methodologies) and is likely to result in a more harmonised and timely opinion from both agencies (that also takes account of the most recent evidence).Proposed change (if any): |  |
| 318-321 |  | Comment:EFPIA supports retention of the existing nested item structure, as developed through the item reduction process. There is external evidence that having multiple items asking similar questions increases the internal consistency of the measure. The rationale and supportive literature for this: Internal consistency reliability (Cronbach’s alpha) can tell us about groups of items within the instrument thought to measure different aspects of the same concept. The use of several items allows for a more reliable scale and richer information about the patient experience. (*Litwin* 2nd ed, “How to Assess and Interpret Survey Psychometrics,” from: ‘The Survey Kit v2.0 2003’ (Arlene Fink, series editor) |  |
| 569-575 |  | Comment:EFPIA feels that the removal of daily physical activity based on ‘Item Response Theory’/Rasch analysis was appropriate as described aboveProposed change (if any): |  |
| 640-641 |  | ‘Physical Activity remains an important component to evaluate. Whilst physical activity did not fit within the conceptual framework underpinning the EXACT, other measures of Physical activity and of capacity for exercise (such as exercise endurance tests) can be used to evaluate this in parallel with the EXACT PRO, with appropriate attentuion paid to study design and patient burden. Therefore, EFPIA feels this does not need to be mentioned in the final qualification opinion - it is more appropriate to keep it in the EMA ‘Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD)’ |  |

Please add more rows if needed.