5 January 2015

Submission of comments on 'Draft concept paper on the revision of the guideline on the development of new medicinal products for the treatment of ulcerative colitis’ – EMA/CHMP/327812/2014

Comments from:

| Name of organisation or individual |
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*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 welcome the opportunity to provide comments on this Concept Paper on the revision of the guideline on the development of new medicinal products for the treatment of ulcerative colitis (CHMP/EWP/18463/2006). We have identified a few major comments we expect to be addressed in the forthcoming finalised guideline:1. **‘Induction of disease remission’ and ‘maintenance of remission’ vs. ‘treatment of disease’ indication:**

We support EMA’s intention to revisit the historic paradigm for studying induction and maintenance of remission, and would encourage that the guidance allow flexibility on treatment indication and in trial design that is appropriate for the compound under study and the desired claims.1. **EMA position on histological assessment *vs*. endoscopic assessment for evidence of mucosal healing:**

In our view, histology is not validated, nor are procedures to obtain samples over time.  Exact locations cannot be duplicated longitudinally.  Endoscopic visualization is feasible however inclusion criteria can have consequential effects on enrollment.  Minimal amount of mucosal inflammation along with some symptoms (abdominal pain, stool frequency, CDAI) should drive enrollment criteria.  Central confirmation may underestimate mucosal inflammation thus making enrollment even more challenging.  Endoscopy continues to be challenging in children:  the bowel prep being the most obtrusive to families and school-aged children.Clinical response would be more appropriate as a meaningful primary endpoint for induction (especially for young people with UC who have failed biologicals) and probably for maintenance also.1. **Global Regulatory Agency Collaboration**

We acknowledge that other Regulatory Agencies worldwide are also considering the same kind of re-examination of Inflammatory Bowel Disease trial designs and endpoints. We recognize the need and desire for autonomy between Agencies to best suit local regulatory needs. However, we would also urge close collaboration between Agencies in this re-examination process to avoid an outcome that would require mutually exclusive study designs or substantially different primary endpoints that would make it difficult to conduct single, consolidated pivotal programs that will satisfy all major global Agencies’ requirements for medicinal product approvals for new IBD treatments.There are also growing discussions in both the EU and US paediatric community and within regulatory agencies on the desire for more up to date requirements in this area. The proposed revisions and an attempt to align the requirements globally would be valuable steps forward in the development of medicines in this area. Since the FDA organised 2 workshops on Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics in September 2012 and October 2013, respectively, we would appreciate the conclusions from these workshops be taken into account in the revised EU guideline in order to facilitate global development.Detailed comments are also provided below in section 2 - “Specific Comments on the text”.  |  |

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)* |
| --- | --- | --- | --- |
| Lines 32 and 82-83 |  | **Comment:** Recommendation does not specify if comparators will be addressed in first line or add-on treatments in different disease populations (e.g. mild or moderate-to-severe population). Current guideline does not address with sufficient detail comparators in second-line or moderate-to-severe population who are not well controlled with immune suppressants (i.e. azathioprine; 6- mercatopurine) or biologic therapy. Please consider addressing comparators similar to current EMA RA guidance (CPMP/EWP/556/95rev1/final), which delineates comparators by disease severity and intended use of the new agent in the disease treatment paradigm.**Proposed change:** Please consider the following addition to the problem statement (after line 32) - ***Additionally, with a shift in the treatment paradigm in the moderate-to-severe population, appropriate comparators for add-on therapy needs to be considered.*** |  |
| Lines 34-40*Endpoints in clinical trials in adults and children* |  | **Comment:** **Mucosal healing as an endpoint**Morphological endpoints to measure mucosal healing would be acceptable for adults from a practical perspective; however, the important issue is the need for standardization and clear definition of the acceptability of such an endpoint to CHMP. Assessment based on endoscopic appearance may not correlate with assessment based on histological findings, and there is no clear guidance on whether endoscopic or histological assessment is required for demonstrating such an endpoint. Furthermore, there is not yet a consensus on the instruments used for such an assessment, whether endoscopic or histological, and there is no consensus on the definition of “mucosal healing.”The utility of central reading of endoscopy examinations in UC is still of unproven value. While it may enhance qualification of a subject into a trial of mild-to-moderate UC population and thereby improving detection of a treatment effect, this potential benefit of central reading has not been shown in trials of moderate-to-severe UC population. Employing central assessment of endoscopic appearance has not been shown to reduce variability. If central reading is recommended it would be important to clarify the overall rationale as to why it is considered valuable. Furthermore, it is important for the agency to provide guidance on the methodology of central reading (including, for example, considerations on single versus multiple central readers and the resolution of discrepancies).It would also be useful to note in the guideline that placebo rates can be high if there is a short wash out prior to the first endoscopy.**Clinical response as an endpoint**Clinical response would be more appropriate as a meaningful primary endpoint for induction (especially for young people with UC who have failed biologicals) and probably for maintenance also.**Biomarkers**We agree that biomarkers (such as C-reactive protein and faecal calprotectin) can be helpful indicators of clinical outcome. However, their utility in assessing response to treatment is limited. With regards to the proposed biomarkers, it should be clarified if the proposal is to use biomarkers as a means to enrich the patient population as a companion diagnostic (in which case there should be additional consideration if, for example, inclusion criteria adversely impacts screen rate), or as part of the primary measure of efficacy. **Paediatrics**For paediatrics, use of repeated endoscopy may be more difficult to gain acceptance of by the investigator and patient/parent community. Consideration could be given to restricting this to the start (screening at induction start) and end of study (end of maintenance). The paediatric ulcerative colitis activity index was specifically validated first with an endoscopic component and then specifically without the endoscopic components. These cross-validation studies showed the endoscopic component do not add additional value in assessing disease activity.Although demonstrating mucosal healing may have some appeal in parallel to the growing trend in adult studies, there are practical considerations that make the assessment of mucosal healing as the primary or even a required secondary endpoint in pivotal clinical trials in children with UC undesirable. A mucosal healing endpoint, by definition, requires sigmoidoscopy or colonoscopy at both baseline and at study completion. For the most common duration of induction studies, this would mean performing two invasive procedures in the span of 8 weeks or less. This would substantially increase the barrier to enrolment, especially in younger children, by parents reluctant to commit their child to two invasive procedures in a short time span, especially in children who may feel quite well at the end of treatment, even at the end of maintenance after 52 weeks. Young children may require heavy sedation or even general anaesthesia in some cases to accomplish safe completion of the endoscopic procedure. As the lower age limit for inclusion moves downward, this enrolment barrier will become especially high in recruiting these difficult to enrol trials. Mucosal healing should be included as an optional key secondary endpoint for the purposes of specific supplementary labelling in children, but not as a required primary or secondary endpoint.Finally, it is suggested that mucosal healing should be assessed by imaging studies and not by endoscopy. Indeed, parents would not appreciate invasive procedures such as endoscopy/colonoscopy for their children if it could be avoided. |  |
| Lines 41-50*Extrapolation of data from studies in adults to the paediatric situation*…and lines 84-86…and lines 87-88 |  | **Comment:** Clear guidance is needed to indicate when separate data in children is needed for the development of a new product for the treatment of Ulcerative Colitis.Consideration should be given to providing guidance on extrapolation of adult exposure-response for clinical efficacy, for the design of paediatric efficacy trials, in the context of the current state of knowledge with regards to differences in the disease and response to therapy between adults and children. Even when stand-alone paediatric trials are necessary, utilization of adult exposure- response information will enable more efficient and optimal paediatric efficacy trial designs, for example, by reducing the need for dose-ranging. Consider guidance on such “partial extrapolation” approaches to optimize the design of paediatric efficacy trials, especially in relation to the number of dose arms evaluated. While stand-alone paediatric trials may be currently required in UC (or Crohn’s Disease (CD)), given limited available data to inform assumptions underlying extrapolation, sponsors should be encouraged to utilize emerging data to further inform extrapolation assumptions and propose more efficient alternative paediatric program designs based on appropriate rationale. In this context consider guidance on how accumulating information from paediatric trials completed in future may further inform underlying assumptions for extrapolation, such as similarity of response to therapy. Ongoing collaboration between EMA and industry would be very helpful in this regard. Additionally, guidance on bridging of newer efficacy endpoints from adults to children should be provided, in the context of evaluating the underlying assumptions for extrapolation.Although it is important to evaluate pharmacokinetics (PK) in the population, separate PK or pharmacokinetics / pharmacodynamics (PK/PD) studies in the patient population are typically not feasible because (1) they are short-term studies and do not provide a therapeutic benefit, thereby limiting enrollment, and (2) they may result in significantly longer development programs. Guidance should be provided on designing paediatric efficacy trials where PK information in the patient population can be obtained in the same trial, and utilize any new information in an adaptive fashion in the trial. In addition, guidance on the extrapolation of PK data obtained from paediatric patients with other inflammatory conditions (such as juvenile idiopathic arthritis, psoriasis, CD) to paediatric patients with UC, based on the historical comparability of PK characteristics in these populations in the context of route of administration, clearance mechanisms, and relationship of PK with body weight and age, should be taken into consideration. Consider sharing EMA’s review experience regarding differences in PK/PD between adults and children, to provide sponsors a better understanding of potential concerns. Analysis of available PK/PD data in adults and children across medicinal products and medicine product classes may help broadly define criteria for extrapolation.**Comment:** In paediatric trials, the incorporation of invasive endoscopic procedures in the paediatric population should be considered, but only after there is adequate data generated from adult studies to justify mucosal healing/histology as the gold standards for treatment efficacy. Non-invasive biomarkers (serum and faecal inflammatory markers), along with patient and physician symptom scoring tools should be used as primary outcome measures in paediatric subjects.**Proposed Change:**In recommendation 2 please consider including: 2.) The need for more clear guidance as regards the possibility for extrapolation from adults, or the need to generate separate data in children. In the latter case, the scope of the studies needed, including design, ***role/appropriateness of endoscopic/histological endpoints*** and comparators need to be described. |  |
| Lines 51-63*Design of the studies in children* |  | **Comment:** In the absence of any paediatric data, we need to assume a similarity of PK-PD or exposure-response relationship between adults and children for initial dose selection / PK studies. This is a reasonable assumption for UC based on the scientific literature. Results of the dose selection / PK studies would provide paediatric data to assess the validity of the assumption.We are aware that there is some resistance to conducting placebo controlled studies, however, the challenges of selecting comparators and powering studies appropriately in a limited patient population should not be ignored. Allowing flexibility in the guideline for alternative study designs is therefore critical, as enforcing too restrictive conditions may drive focus of development elsewhere (aside from meeting mandatory Paediatric Investigation Plan (PIP) requirements). The guideline should not be overly complex or lack the variance in clinical practice. The use of an active comparator poses several difficulties in children, such as placebo infusions / injections (which can be an onerous burden that few subjects / parents / guardians are likely to accept and not resolvable by open label design), inclusion of specific treatment failures which may render the treatment population more refractory than desired or even introduce bias, and statistical considerations (numbers in the hundreds and/or uncertainty over acceptable margins even if studies are acceptable as “estimates”). Therefore, we believe that a blinded, active comparator should not be required for UC trials in children. Some considerations in the guideline could include suggestions that designs should be allowed to vary depending on the nature of the agent (small molecule, biologic treatment) e.g. non-equivalent study designs (biosimilar-type approach), comparators as in-study controls, or clearer treatment discontinuation criteria (escape rules) in placebo controlled studies. It might be also useful to evaluate whether failure of immunosuppressants should still be required to select for the study population (Walters et al. Gastroenterology. 2014;146(2):383-91). |  |
| Lines 51-63*Design of the studies in children* |  | **Comment:**The current guidelines states that the paediatric UC population ranges from 2-18 years. It should be noted that within the paediatric population diagnosed before the age of 6 years (very early onset IBD or VEO-IBD, diagnosed as early as the newborn) patients present with severe colonic disease, have distinct disease pathology (including genetic polymorphisms) and usually do not respond to standard therapies, including biologics. This specific and rarer population should be excluded from general paediatric studies in IBD.Additionally, paediatricians would like to accelerate investigation of promising therapies in paediatric population, however, the hurdle very often is lack of age-appropriate clinical and pre-clinical toxicology assessment**Propose Change (if any):** We suggest allowing studies to enrol older children (e.g. adolescents age 13-18), once there is sufficient safety & data obtained from the adult population (perhaps include adolescents in phase 3).Additionally we recommend addressing specific guidance on paediatric studies for ages 0-6 yrs, 7-12 years and 13-18 years (adolescents) in the concept paper and guidance (with some discussion of the appropriateness of PK-PD extrapolation). We recommend excluding patients 0-6 yrs from paediatric studies because they are a rare and distinct population with a unique disease pathology (see above). |  |
| Lines 64-76*Design of studies (in both adults and children)* |  | **Comment:** EFPIA are supportive of the flexibility for either approach (i.e. separate or combined induction and maintenance studies), thereby allowing study designs and endpoints to be developed appropriately for mechanism/onset of action. This is a positive development and may potentially lead to new and more efficient treatment paradigms, allowing the use of new medicinal products to their full potential.In addition, the current guideline calls for at least two well controlled studies for establishing efficacy. In practice it is common to see one combined induction and maintenance study and one induction only study in phase 3 to support both induction and maintenance claims. With this in mind we recommend considering the following addition to lines 74-76:“...A reflection of the possible claims for new substances goes along with the reflection and potential changes of the trial designs and ***overall requirement of efficacy evidence to support approval in ulcerative colitis***...”**Induction Endpoints**Clarification is needed on whether induction endpoints are still required if the induction/maintenance studies are merged into one study (a baseline and week 52 endpoint may alleviate the requirements for multiple endoscopies). Clarification is also needed on requirements for re-randomisation i.e. that interim endpoints (e.g. Wk 6/ Wk 8 and Wk 52) are acceptable without re-randomisation into the maintenance phase. The acceptability of both these points from a regulatory standpoint should be made clear in the guideline, albeit acknowledging the potential difference in label wording. |  |
| Line 82-83 |  | **Comment:** The discussion section of the concept paper has a significant piece on mucosal healing in induction and remission and this is not reiterated in Recommendation 1 on endpoints in lines 82-83. It is expected the following will be included in further consideration:**Proposed change:** 2) The examination and potential revision of the recommendations for the primary and secondary endpoints ***(including the assessment of mucosal healing through endoscopy and/or histology)***, and for the principal design of the trials (including the comparator to be used). |  |

Please add more rows if needed.