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EMA/760013/2015
Committee for Medicinal Products for Human Use (CHMP)

Submission of comments on 'Qualification Opinion of Paediatric ulcerative colitis activity index (EMA/CHMP/SAWP/485560/2015)

Comments from:

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1. General comments

Stakeholder number *(see cover page)*	General comment (if any)	Outcome (if applicable)
1	Overall, we would like to convey our support for the proposals in the draft qualification opinion to more formally recognise that the PUCAI has been validated for disease classification and as a primary clinical outcome measure in clinical trials for paediatric ulcerative colitis. The document provides several useful considerations for this important and emerging area. Given the data available on the use of the PUCAI, we add our support to its validity and wider usage. Additional points that would be helpful to clarify are discussed as follows: • The description of the potential conditions for extrapolation of the effect on mucosal healing to paediatric clinical trials and thereby waiving endoscopy is particularly vague. Acknowledging the statement that this topic is outside the scope of this qualification opinion, is EMA planning to provide further guidance in this subject? • It would be useful to provide further guidance on the lower age cut off for children as part of the inclusion criteria (e.g. aged around 6)	The comments refer to several points proposed to widen the scope of the qualification opinion, which is overall not considered adequate. This is commented upon in the following: a) Extrapolation is a completely distinct approach in paediatric IBD, which is not related to the qualification of an outcome measure, which itself implies the conduct of studies. Therefore, any statements on extrapolation are not needed. Further guidance for extrapolation will be dealt with in the general guidance planned to be published for extrapolation, and in the ongoing revision of the IBD guidelines (EMA/129698/2012 and EMA/CHMP/327812/2014) b) Similar to the problem of extrapolation, the problem of age cut-off for patients to be included into paediatric clinical trials in IBD is itself not a problem of the PUCAI, but a general question of the UC guideline.

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	• As a minor comment, it would be useful to add the ECCO statement (Ruemmele FM,Hyams JS, Otley A, et al.Gut doi:10.1136/gutjnl-2014-307008), that has been referred to in the text, to the list of references.	c) Agreed. The list of references will be complemented.
2.	The European Crohn's and Colitis Organisation's (ECCO) main mission is to improve the care of paediatric, adult and elderly patients with Inflammatory Bowel Disease (IBD) in all its aspects. It is, therefore, a key perspective also to share opinions and common strategies with the European Medicines Agency (EMA) with the final aim to deliver a better service to European IBD patients. In this regard, ECCO recognizes that any effort aiming to implement and finally to improve paediatric IBD would be worthy of support and collaboration. Because of this and in view of a mutual advantage of current growing collaboration, ECCO is extremely motivated to provide pertinent observation. In this context, it is widely recognized that treatment of paediatric IBD patients poses specific challenges and entails age specific hurdles, such as the delay in licensing of new efficacious medications with already proven benefit in IBD adult patients. In particular, same as Applicants stated, ECCO recognizes that the primary outcome of UC clinical trials in adult patients should be based also on the evaluation of colonic mucosa. The paediatric population, however, raises some particular	

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	considerations (e.g. small eligible population to recruit, safety parents' concerns, clinician hesitancies with regard to invasive procedures) which may place ethical issues and challenge trial feasibility. At the same time, ECCO supports that the advantage of paediatric trials as "confirmatory" of similar trials in adult IBD patients should be adopted to balance the above mentioned recruitment challenges. Therefore, it would be extremely important to adopt suitable outcome measures in order to increase feasibility of paediatric IBD trials.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome
275-277	1	Comment: What would be defined as appropriate justification for waiving colonoscopy? On page 2 the example of 'therapies already shown to induce MH in adults' is given.	See previous comments. The scope of the qualification is deliberately kept outside of the scope of the definition of an adequate justification of extrapolation. The example as of page 2 was given by the applicant. It was deliberately not included in the final statements for the context of use.
278-279	1	Comment: Where endoscopy is the primary outcome, what is the expectation that this assessment will be based on in order that PUCAI would be allowed to be used for efficacy evaluation? Would it still be expected that the inclusion criteria are based on either PUCAI or endoscopy?	See previous comments. The qualification of the PUCAI does not deal with the use of the PUCAI as efficacy outcome in a situation when endoscopy is available as primary outcome.
Line 275-277	2	Comment: "1. The paediatric ulcerative colitis activity index (PUCAI) can be used as the primary outcome measure in clinical trials of paediatric UC as a proxy for endoscopic assessment when colonoscopy is waived with appropriate justification." As the PUCAI has shown high correlation with the endoscopic appearance of colonic mucosa and with the Mayo score in multiple studies and because of the above reasons (see general comment), ECCO fully supports the statement. Proposed change (if any): No proposed change.	The support is noted.
Line 278-279	2	Comment: "2.The PUCAI is suitable to be used as reliable efficacy evaluation in visits during which endoscopy is not performed in clinical trials of paediatric UC where endoscopy is used as primary outcome." As the PUCAI has shown higher	The support is noted.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome
		discriminative validity in differentiation of clinical remission and various grade of disease activity than other commonly used clinically activity indices, high correlation with endoscopic outcomes with various therapeutic agents, higher predictive value than commonly used biomarkers (e.g. CRP, faecal calprotectin), prediction of need for dose escalation, for 1-year steroid-free remission and for 1-year salvage therapy, ECCO fully supports the statement. Proposed change (if any): No proposed change.	
Line 280-281	2	Comment: “3. The PUCAI can be used to screen paediatric UC patients in order to grade disease activity into mild, moderate or severe.” As the PUCAI presents definite cut-off scores of remission, mild, moderate, severe disease that have been validated before treatment in several cohorts (paediatric and adult IBD patients) and have been found to have high sensitivity, specificity and area under the ROC curve >90%, ECCO fully supports the statement. Proposed change (if any): No proposed change.	The support is noted.