26 January 2017

Submission of comments on: Guideline on the clinical investigation of medicinal products for the treatment of Ulcerative Colitis - CHMP/EWP/18463/2006 Rev.1

Comments from: EFPIA

| 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) ordered comments by topic appearance in document* |
| --- | --- | --- |
|  | The guidance is comprehensive and incorporates many of the recommendations made in the review and comment process on the UC Concept Paper from 2014. The guidance however omits consideration of Response Rates in the induction or remission phase of disease treatment as a primary efficacy endpoint for approval. This appears to overlook the importance of response to therapy in the moderate to severe population. It also does not seem to be aligned with attaining the indication for “treatment of active ulcerative colitis” as described in section 5 ‘ Indications/treatment goals’. It is our position that a pre-defined ‘Response’ criteria can represent clinically meaningful “treatment of active ulcerative colitis” and we would recommend CHMP consider incorporating language into the guidance relating to ‘Clinical Response’ as not only a secondary endpoint but a primary endpoint for pivotal registration trials.  |  |
|  | We welcome the availability of these updated guidelines. However, we have 3 main areas of concern, where the EMA proposed changes to the guidelines would dramatically affect the availability of new and potentially effective medications for Ulcerative Colitis and Crohn’s disease in the European Union. We view that this is contrary to the EMA’s mission to “facilitate development and access to medicines”, leading to “timely patient access to new medicines”.1. ‘Maintenance of remission/Prevention of relapse’: primary endpoint of “**maintenance of corticosteroid-free remission without surgery throughout at least 12 months**”

The Agency’s suggested primary endpoint of “maintenance of corticosteroid-free remission without surgery throughout at least 12 months” is a laudable aspiration, but is not a feasible endpoint for currently available medications. Mandating this endpoint in the EU will impose a requirement for very large maintenance cohorts, with treatment durations of longer than 12 months, making both the size and cost of maintenance studies unfeasible. 1. **Co-primary endpoints**

Draft UC Guidance suggests a “Co-Primary” endpoint approach that considers both symptomatic relief as well as an effect on the inflammatory process rather than the more commonly used Composite indices, such as the Mayo Clinical index. In the FDA’s Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry released Aug 2016, a **composite** endpoint which includes an assessment of signs and symptoms and endoscopic improvement is proposed.Our views that the diverging definitions of the primary endpoints could prove to be problematic and a shift to a more consistent desired primary endpoint definition between regional guidance would be of benefit to patients.1. **Design of maintenance trial**

Including only remitters in the primary analysis makes the sample size needed in induction infeasible; the induction phase is not anticipated to be long enough to wean patients from steroids, and finally, many patients that are responders and not remitters at the end of induction achieve remission by the end of maintenance. |  |
|  | While we are supportive of EMA draft guidance, one topic that we believe the guidance should discuss in greater detail is the treatment of patients that have been previously exposed to other therapies. For sponsors, it is critical to have clear expectations from the EMA because the mucosal healing in these hard-to-treat patients is very likely to be reduced. Because the definitions of response have been altered, new drugs that offer incremental benefits to patients who are without remaining treatment options may no longer be pursued by sponsors. Historical evidence demonstrates that improvements in the pharmacological treatment of patients with ulcerative colitis occurred in small steps, yet these products were welcomed by patients and physicians because they represented additional treatment options even though they may not be considered “transformative” products. |  |
|  | As the draft guideline states, UC is rare below 10 years of age. Yet the clinical development is asked to include patients from 2 years of age. Fully-powered clinical efficacy studies in the paediatric population 2 – 10 years of age might not be feasible due to the low patient numbers. Therefore clarification is needed on what is expected to be demonstrated in those children.  |  |
|  | **Comments:** It would be helpful to understand if EMA recommends any specific guidance to be followed when developing and validating PRO instruments. Examples are the Good Practice in Outcomes Research from the ISPOR or other institutions and the U.S. FDA “Guidance for Industry Patient-Reported Outcome Measures: use in Medical Product Development to Support Labeling Claims”. |  |

1. Specific comments on text – Major Comments

| 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)* |
| --- | --- | --- | --- |
| 98-110 |  | **Comment:** Please clarify if the extent of active ulcerative colitis needs to be assessed at entry into study or if historical extent of active disease is acceptable |  |
| 102-103 |  | **Comment:** Histological evaluation might be part of the differential diagnosis of UC. Our data suggest that more than 80% of subjects with a Mayo endoscopy score of > 2 (current eligibility criterial applied in biologic trials) present with histologically active disease. Therefore, we believe that a Mayo endoscopy score >= 2 is a surrogate for histologically active disease at screening. We do not believe that a separate inclusion criterion related to histologic confirmation of UC activity is necessary. |  |
| 123-124 |  | Clinician feedback has indicated that it is not necessary for patients to receive 3 months of treatment with thiopurines in order to know if someone is going to be refractory to those agents. While achieving the full extent of response to thiopurines may take 90 days, it is possible to know much earlier (e.g., within 30 days) if someone is going to respond to these agents at all. **Proposed Change**: Please change “3 months” to “6 weeks.”  |  |
| 125 |  | **Comment:** A working definition of “Remission” is proposed to be based on endoscopic mucosal healing, with no or very mild signs. See proposed change below. Suggest making definition(s) of remission consistent with those used in clinical practice and also FDA draft guidance. **Proposed change (if any):** The authors should consider defining a number of different types of remission, including (1) clinical remission, as suggested above, (2) endoscopic remission [Mayo endoscopic subscore of 0-1 or absence of friability and erosions on UCEIS), and (3) histologic remission. |  |
| 131-132 |  | **Comment:** Why is the indication “treatment of active ulcerative colitis” and not “treatment of ulcerative colitis”, as it includes maintenance of remission? Why only “maintenance of remission” and not “remission or sustained remission”?**Proposed change (if any):** In order to obtain an indication for “treatment of ~~active~~ ulcerative colitis”, efficacy in both “induction of remission” as well as “~~maintenance~~  **remission or sustained** **~~of~~** remission” should be demonstrated. |  |
| 131-141 |  | **Comment:** The rationale for requiring separate investigation of induction and maintenance in order to achieve separate induction and maintenance claims; and why certain study designs are acceptable and others are not acceptable, are unclear in the guidance. This current text also suggests that a treat-through study design that demonstrates efficacy in both induction of remission and sustaining remission is not a suitable design to obtain the label claim of “treatment of active ulcerative colitis”While the short-term goal of treatments is to achieve rapid symptom relief (induction) and the long-term goal is to maintain control of the disease (maintenance); in clinical practice there is not a fixed duration induction phase and a fixed duration maintenance phase. Clinical practice embraces a more holistic approach, where patients will be treated with an intervention until it is clearly evident that the intervention does not result in benefit. With respect to the use of biologic treatments, the initial assessment of whether there is/ is not sufficient clinical benefit to justify continuing treatment could take a few months. This timeframe is consistent with the estimated peak/ steady state of maintenance PKPD effect to be achieved across different approved MOAs (~12-20 weeks). If sufficient initial benefit is achieved, patients will continue to be maintained on that treatment for a longer time, with ongoing observation to ensure there is sustained benefit.Enforcement of a strict induction and maintenance study paradigm (i.e. induction followed by randomization to active drug maintenance or withdrawal to placebo) without consideration of the time to achieve optimal PKPD effects will limit our ability to evaluate the true efficacy potential of a given MOA, because patients who “are not induced” into response will not continue into the randomized maintenance trial. Historically, biologic trials have studied induction efficacy at time points ranging from 2 weeks to 12 weeks; and most of these trials have reported that a substantial proportion of patients may achieve a delayed response to induction (i.e. the non-randomized population in the randomized withdrawal maintenance study).Thus, a treat-through design, which evaluates efficacy from a population perspective, would provide a much more accurate assessment of the real efficacy potential of a MOA, both short-term and long-term.Additional comments regarding the appropriateness of treat-through vs. randomized withdrawal maintenance studies are provided in response to Lines 340-353.**Proposed change (if any):** Please address the appropriateness of a treat through design to demonstrate efficacy and at a minimum add an additional sentence at line 132. “A treat-through study design showing efficacy in both “induction of remission” and “sustained remission” may be suitable to obtain an indication for “treatment of active ulcerative colitis”.  |  |
| 136-141 |  | In regard to the recommendations favouring separate induction and maintenance studies, it should be noted that comparison to standard of care comparators (eg anti-TNF) using this methodology incurs substantial complexity. Similarly, when active comparators are used, potentially nonsensical treatment regimens may be necessary to maintain study blinding in randomized withdrawal designs. We believe comparison to SOC in both induction and in maintenance may be best accomplished using a treat through methodology. |  |
| 138 |  | **Comment:** While a “treat -through” design may be acceptable the design of the study will have implications for the indications that can be claimed.While it is clear that indication for “treatment of active UC” can be obtained with adequate demonstration of effect in both induction and maintenance, and that separate demonstration of efficacy in induction and demonstration of efficacy in maintenance may lead to separate indication for induction and maintenance respectively, it is not clear what indication may be granted when using a treat-through design**Proposed change (if any):** Pleaseclarify the type of indication granted in case of treat-through design.Also further define “treat-through”  |  |
| 147-148 |  | There are drugs in development for UC that do not have a direct effect on inflammation; it would be helpful if the guidance would consider other mechanisms that may have a benefit to patients (e.g., drugs that directly promote mucosal healing) |  |
| 152-159  |  | **Comment:** The revised guideline encourages use of a PRO instrument for the use as primary outcome parameter in clinical trials in UC which includes “clinically important signs and symptoms of UC”. In clinical outcome assessment research, a sign is an objective aspect of a condition or disease that can be observed or measured. A symptom is subjective from the patient point of view and represents what the patient experiences about the condition or disease; they are not able to be observed or measured objectively. Signs can be evaluated using a PRO but are more commonly evaluated/reported by the physician/investigator who uses their medical training and judgement to score the sign (a so-called Clinician-reported outcome, or ClinRO). The Mayo score is an instrument that contains both signs and symptoms, but the signs are evaluated and reported by the physician/investigator (ClinRO), while the symptoms are evaluated and reported by the patient (PRO). **Proposed change (if any):** Can the agency confirm whether the co-primary endpoint should be (a) symptomatic remission, using PRO data on symptoms only, (b) remission of signs and symptoms, as reported using a validated PRO which encompasses both, or (c) remission of signs as reported using a validated ClinRO and symptoms as reported using a validated PRO? |  |
| 152-159  |  | **Comment:** It is encouraging that the EMA continues to consider the measurement of patient-reported symptoms of UC as a co-primary endpoint in establishing treatment benefit. It is acknowledged that the patient perspective is key in defining signs and symptoms which are important to evaluate and concur with the Agency that a patient-reported outcome (PRO) instrument to be used as primary outcome measure in pivotal clinical trials in UC should be “completely and rigorously validated”. When defining validity in PRO instruments, the Reflection Paper on the regulatory guidance for the use of Health-Related Quality of Life (HRQL) measures in the evaluation of medicinal products (CHPM/EWP/139391/04) alludes to validity, reliability, responsiveness and interpretability for the specific condition/setting. Numerous good practice guidelines have been developed on PRO instrument validation since the release of this guidance document (ISPOR, FDA etc) – can the agency clarify the evidence they are looking for to support the consideration of a PRO instrument as “completely and rigorously validated”**Proposed change (if any):** |  |
| 152, 166-167 |  | **Comment:** Please use “patient reported outcomes” and not “patient related outcomes”**Proposed change (if any):** “Symptomatic relief should be evaluated by patient ~~related~~**reported** outcomes (PRO).”“The use of this index may be justified, however, as previously mentioned, an effect on both the patient ~~related~~ **reported** sub-score and the endoscopic score is expected.” |  |
| 152-159 |  | **Comment:** The current text referring to symptomatic relief in section 6.1 states...’ Symptomatic relief should be evaluated by patient related outcomes (PRO). There are a number of clinical indices, e.g. SCCAI (simple clinical colitis activity index) mainly including patient reported symptoms. Whereas these may be used provided that they are adequately validated, this guideline recommends the further development and validation of PRO instruments for the use as primary outcome parameter in clinical trials in UC. Such an instrument should include clinically important signs and symptoms of UC, e.g. increased stool frequency and rectal discharge of blood. An instrument to be used as primary outcome measure in pivotal clinical trials in UC should be completely and rigorously validated.’... This omits reference to the domains of the Mayo Score that has been used previously in clinical trials, and has ambiguity in its recommendation and should be updated.**Proposed Change:** We proposed the following updated text.‘Symptomatic relief should be evaluated by patient ~~related~~ reported outcomes (PRO). There are a number of clinical indices, e.g. SCCAI (simple clinical colitis activity index) *and Mayo Scoring Tool that include assessment* of patient reported symptoms *but current signs and symptoms scales are not considered adequately validated.* This guideline recommends the further development and validation *of PRO* instruments for use as primary outcome parameter in clinical trials in UC. Such an instrument should include clinically important signs and symptoms of UC, e.g. ~~increased~~ stool frequency and rectal discharge of blood. An instrument to be used as primary outcome measure in pivotal clinical trials in UC should be completely and rigorously validated. |  |
| 164-167 |  | Please note that the Mayo score is a composite scale. Is the statement that co-primary endpoints (PRO plus endoscopy) are required intended to remove use of a composite index that includes both PRO plus endoscopy, such as the Mayo score? Will sponsors now need to show impact on both parameters separately? Is the use of the stool frequency and rectal bleeding subscores as one co-primary endpoint and use of the endoscopic subscore as another co-primary endpoint recommended? |  |
| 164-168 |  | **Comment:** We advocate the continued use of the total Mayo score (including PGA) until new PRO endpoints/criteria have been validated. Furthermore, the continued collection of the total Mayo score will be necessary to compare data collected in active comparator studies (e.g. where the reference arm is infliximab) where the historical data for the reference arm is based on efficacy demonstrated using the criteria of the total Mayo score. **Proposed change:** Delete or preface the statement in lines 167-168 which discourages the use of the total Mayo score as a primary interest in future studies with clarification of when use of the total Mayo score might be appropriately acknowledged.  |  |
| 169-170 |  | **Comment:** Please indicate if the EMA considers endpoints that include surrogate markers of inflammation suitable to use as secondary or exploratory endpoints. Will the inclusion of surrogate markers of inflammation lead to additional language in the label?**Proposed change (if any):** See above. |  |
| 172-192  |  | **Comment**: The revised guideline clearly indicates that “remission” of signs and symptoms is the preferred way of scoring the PRO used to support a co-primary endpoint. This is contrary to a recent marketing authorisation approved by EMA for Entyvio (vedolizumab) in May 2014 in which the primary endpoint for induction of remission was clinical response defined as a reduction in Mayo score of ≥ 3 points and ≥ 30% from baseline and a decrease in the rectal bleeding subscore. As the trial enrolled moderately to severely active UC patients with a Mayo score 6 to 12, some patients would have been defined as clinical responders based on less stringent criteria than is being now proposed i.e. with an endpoint score >1. We believe that this less stringent criteria, representing “decreasing the severity of UC” employed in the Entyvio development program remains clinically relevant for patients and should be considered as an additional parameter on which to define treatment success beyond remission.**Proposed change (if any):** Agency to clarify if clinical response can be accepted as primary endpoint  |  |
| 173 |  | **Comment:** Achieving steroid free remission is an appropriate endpoint in clinical trials and in clinical practice. However, it is not an appropriate primary endpoint in induction, as (i) not all patients will be on steroids on entry to the study, and (ii) subjects will often remain on a fixed dose of steroids throughout the induction period, with protocolized weaning after achieving response or remission at the end of induction. Thus, in many trial designs, it is impossible to achieve this endpoint at the end of induction. The proposal ignores the substantial clinical benefit that many subjects gain by achieving clinical response. Furthermore, this proposal will lead to unfeasibly large and expensive clinical trials and act as a disincentive for conducting clinical trials in IBD, to the detriment of this patient population with substantial unmet need. **Proposed change (if any):** Consider changing steroid free remission to “an appropriate goal of treatment and an appropriate secondary endpoint”. |  |
| 173-176 |  | **Comment:** Text in lines 173-176 does not include text regarding induction/maintenance of a clinical response ‘Achieving/maintaining remission free of steroids is an appropriate primary end-point. In patients receiving systemic steroids these should be tapered according to predefined schedules. For induction studies of short duration requiring early evaluation of efficacy a low dose of steroids may be acceptable provided that the dose is clearly justified and pre-specified.’**Proposed change (if any):**Achieving/maintaining remission free of steroids is an appropriate primary end-point. *Alternatively achieving/maintaining a clinical response based on a clearly defined and agreed upon response criteria would be considered as an appropriate primary endpoint.* In patients receiving systemic steroids these should be tapered according to predefined schedules. For induction studies of short duration requiring early evaluation of efficacy a low dose of steroids may be acceptable provided that the dose is clearly justified and pre-specified. |  |
| 174-176 |  | **Comment:** We agree, that when feasible, a low dose corticosteroid is desirable for entry into clinical trials based on several considerations including minimizing the treatment effect due to the corticosteroids and reducing the potential side effects of high dose steroids that are typically maintained at baseline doses throughout the induction period. However, we do not recommend exclusion of patients who require higher doses of corticosteroids as this practice would have the potential to exclude patients who have higher disease activity and therefore limit the ability to understand the effectiveness and safety of the therapy in this more severe population (Ha et al, Clinical Gastroenterology and Hepatology, 2012, 12:1002-1007).**Proposed change:** Delete reference to “low dose” and restate as “….concomitant steroids would be acceptable provided that the dose is clearly justified and pre-specified.” |  |
| 175 |  | Clarity is needed regarding the definition of a “short duration.” It seems reasonable to allow steroids to remain stable during induction studies of up to at least 12 weeks (at a dose of 20 mg/day or less) in order to avoid confounding due to differential rates of taper in the treatment arms. It is not necessarily appropriate to withdraw steroids in a patient who has not yet demonstrated a response to study drug. Also, strict tapering schedules are difficult to define and to standardize given the multiple different corticosteroids available. |  |
| 177-178 |  | **Comment:** Please clarify that signs and symptoms refer to stool frequency and rectal bleeding. Please add definition for signs and symptoms, i.e. stool frequency (SF = 0-1) and rectal bleeding (RB =0)**Proposed change (if any):** **Signs and symptoms are defined by stool frequency (SF = 0-1) and rectal bleeding (RB =0)** |  |
| 184-187 |  | **Comment:** The guidance states :“Correspondingly, when clinical symptoms are evaluated using the clinical part of the Mayo score, a score of 0 or 1 may be used to define symptomatic remission”and“Irrespective of scale used, the definition of remission should encompass cessation of rectal bleeding”.We believe that these two criteria might contradict each other. A Mayo score of 1 could result from the bleeding score of 1 (= “streaks of blood with stool less than half the time”), indicating rectal bleeding.**Proposed change:** Replace recommended definition of remission with the following: “Clinical remission could be defined as a Mayo score ≤ 2 points, with bleeding score=0 and no other individual subscore > 1”. |  |
| 188 |  | **Comment:** The Mayo Clinic Score is composite within a patient. Please clarify whether symptomatic remission and MH is a co-primary endpoint (at population level) or a composite endpoint (within the same patient) and the timing of assessment. Please also clarify whether re-randomization into maintenance is based on a patient achieving either or both symptomatic remission and/or MH.Please also clarify if co-primary endpoints may be assessed at different time points.**Proposed change (if any):**  “As outlined above, symptomatic remission and MH should be considered **composite  ~~co-primary~~** endpoints.” |  |
| 188 |  | The Agency’s Draft UC Guidance suggests a “Co-Primary” endpoint approach that considers both symptomatic relief as well as an effect on the inflammatory process rather than the more commonly used Composite indices, such as the Mayo Clinical index. “A significant effect on both aspects of the disease is required (co-primary endpoints). Composite indices including both symptoms and MH, such as the Mayo Clinic index have been used in several clinical trials. The use of this index may be justified, however, as previously mentioned; an effect on both the patient related sub-score and the endoscopic score is expected. It has to be stressed that the total Mayo score including physician’s global assessment is not of primary interest.”“As outlined above, symptomatic remission and MH should be considered co-primary endpoints. However, as listed below, achieving both symptomatic remission and MH (for the individual patient) is considered an important secondary endpoint. “In the FDA’s Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry released Aug 2016, a composite endpoint which includes an assessment of signs and symptoms and endoscopic improvement. “We currently recommend a primary endpoint of clinical remission (responder definition based on Stool Frequency, Rectal Bleeding, and Endoscopy scores) (see section IV., Interim Approaches to Efficacy Assessments). Until a valid patient-reported outcome instrument for UC signs and symptoms and a valid clinician rating scale for mucosal inflammation in UC become available, a modified Mayo or modified UCDAI score omitting the physician’s global or disease activity ratings, as described in section IV, can be used as an endpoint measure.” (FDA UC Guidance, Sect V.A.)It is Lilly’s opinion that the diverging definitions of the primary endpoints could prove to be problematic and a shift to more consistent desired primary endpoint definition between regional guidance would be of benefit to patients, payers, and sponsors. |  |
| 195 |  | **Comment:** Clinical response (or endoscopic response) is used as a primary endpoint in most published (and ongoing) clinical trials. These are clinically relevant endpoints and the numbers required to show these endpoints are feasible for phase 2 and registration programs. **Proposed change (if any):** Please consider amending the guidance to recommend the use of clinical response or endoscopic response as a suitable primary endpoint in UC clinical trials.  |  |
| 195 |  | **Comment:** Please consider specifying the change in the individual components of a disease activity index that would be appropriate to meet a definition of clinical response or clinical remission. This is included in the FDA draft guidance and was discussed at the FDA’s clinical endpoints conference and the GREAT3 conference.**Proposed change (if any):** Please specify examples of the changes in disease activity index scores required to achieve clinical response or clinical remission, to provide consistency with FDA guidance.  |  |
| 197-200  |  | **Comment**: The revised guideline clearly indicates that “remission” of signs and symptoms is the preferred way of scoring the PRO used to support a co-primary endpoint. This method provides evidence at an individual level (i.e. proportion of responders). However, group level changes (e.g. mean change from baseline) in the PRO will be additional useful information to understand the overall efficacy of an experimental treatment, providing additional data through use of a continuous variable beyond that which can be understood through the creation of a binary outcome. As such, we would like to encourage the Agency to include group-level responses as key supportive/secondary endpoints, (unless already covered under the line 200 “numerical evaluation of the symptoms score”=**Proposed change (if any):** Please indicate whether the endpoints can be analysed as change from baseline  |  |
| 201 |  | Please clarify what scales are appropriate for histological evaluation and at what time point these evaluations are expected |  |
| 201-201 |  | **Comment:** We consider that histological improvement would be an additional valuable secondary endpoint. |  |
| 201-204 |  | **Comment:** We acknowledge that biopsies for histologic disease activity would be collected at screening and post-treatment to assess for subsequent histological healing. However, there is no standardized histologic scoring system, nor is there one that has been validated (Peyrin-Biroulet, L et al. American Journal of Gastroenterology (2015)110: 1324-1338).**Proposed change (if any):** Evaluation of histological improvement should be included as an exploratory endpoint to assess UC activity and treatment efficacy. |  |
| 203 |  | **Comment:** Elevated C reactive protein (CRP) is not a common feature of UC, in contrast to Crohn’s disease. This is not a tractable secondary endpoint. **Proposed change (if any):** Consider removing. |  |
| 203-204 |  | **Comment:** Please clarify if reference is made to faecal calprotectin and not serum calprotectin? If serological, we recommend this being an exploratory endpoint and not included within the composite endpoint, as there is limited data on this. Please clarify what is meant by normalisation of CRP, as many patients do not have elevated CRP levels.Please clarify what label claim this endpoint supports.**Proposed change (if any):** “Patients achieving MH, judged endoscopically, as well as combined clinical, **other biomarkers for** **inflammation ~~serological~~** (eg, ~~=~~**~~normalisation of~~****~~normal~~**CRP and/or **faecal** calprotectin) and histological remission”. |  |
| 208  |  | **Comment**: The revised guidance proposes the use of a validated quality of life (QoL) measurement to support a secondary endpoint related to changes in QoL. The Agency gives examples of both IBD-specific and generic PRO instruments to support this endpoint – does the agency have a preference for one over the other? Most endpoints listed in section 6.1.1.2 provide information on preferred analysis/presentation of results; the QoL endpoint does not. Unlike the Mayo score in which remission can be clearly defined by the absence of signs and symptoms, none of the instruments included in the example have clinically defined criteria for optimal outcomes. As such, can the agency advise on how the endpoint should be developed i.e. mean change from baseline, proportion of patients achieving a pre-defined clinical benefit etc?**Proposed change (if any):** Please indicate any preference the agency may have in terms of endpoint and preferred analysis (e.g. SF-36 and EQ-5D) |  |
| 212 |  | **Comment:** Colectomies are infrequent in 12-52 week clinical trials, particularly when subjects are allowed rescue therapy. Consequently, reduction in the number of colectomies may not be a suitable secondary endpoint for UC clinical trials, outside of the proposed indication of “treatment of acute, severe UC”. **Proposed change (if any):** Consider removing.  |  |
| 213-215 |  | **Comment:** The suggested endpoint of corticosteroid-free remission may be challenging to meet in this difficult-to-treat sub-group and require an unfeasibly large study to have sufficient power to meet this endpoint. Clinical response would be a more feasible primary endpoint in these patients, with corticosteroid-free clinical response as the first secondary endpoint.Clinicians treating patients with UC understand the difference between these endpoints and the implication of achieving each of these endpoints on a per-patient basis. **Proposed change (if any):** Consider changing corticosteroid free remission from a primary to a secondary endpoint for this cohort of patients. Consider avoiding a recommendation for a sub-group analysis of corticosteroid-free remission  |  |
| 213-215 |  | **Comment:** The minimum duration of clinical remission in the absence of steroids required to achieve an endpoint of corticosteroid-free remission is not specified. Feedback from key opinion leaders suggests that a minimum period of 4 weeks is both clinically relevant and important. **Proposed change (if any):** Consider making a statement on the minimum duration of steroid-free remission (or response) required to meet these endpoints.  |  |
| 218 |  | **Comment:** Please clarify the definitions for “mild, moderate and severe”, and how these are measured (i.e. anatomical location versus the Mayo score versus a composite of both).We consider the Mayo score is more appropriate than the anatomical location (i.e. mild=1, moderate=2, severe=3).**Proposed change (if any):** “…e.g. **~~mild, moderate and severe~~** **by MCS, ES, or UCEIS.**” |  |
| 273 |  | **Comment:** Stipulates that subjects entering trials must have had “recent visualization of their GI tract” but does not stipulate what is meant by “recent”.**Proposed change:** Propose recommendation for what is considered "recent".  |  |
| 275-276 |  | If the Full Mayo score is no longer accepted (as noted on line 167-8, which states the PGA component is no longer of interest), then please update this sentence to indicate what is acceptable to define disease for inclusion. Also, is the range specified in this sentence intended to define only moderate to severe disease?  |  |
| 284**Additional related comments:**262-263284 |  | **Comment:** We do not agree with the recommendation that the primary endpoint of an induction study should be steroid free remission.  The reasons to maintain stable corticosteroid doses during the induction period include the following:There would be insufficient time to taper corticosteroids prior to the primary endpoint assessment using the type of tapering schedule generally applied in UC clinical trials. A rapid corticosteroid taper prior to the primary endpoint assessment may precipitate clinical flares that would impact patient well-being and could present challenges to the interpretation of the treatment effect during the induction period. Specifically, a rapid taper of corticosteroids during the induction period could confound the assessment of efficacy in the setting of additional medication changes.  Furthermore, a rapid steroid taper may introduce an imbalance in efficacy in the Placebo vs active treatment group that could result in lower efficacy in the PBO group and would confound assessment of efficacy.  Withdrawal of corticosteroids prior to the induction primary endpoint could also lower the number of patients that may be ultimately eligible for the maintenance study.  In some UC clinical trials, corticosteroid tapering is mandatory in clinical responders using defined criteria over a longer time period during the maintenance period.  Subgroup analyses of induction and maintenance UC trials demonstrated that patient steroid status at study entry did not influence the ability to achieve response or maintain response. These results support the conclusion that meaningful information can be obtained with steroid tapering initiated during maintenance treatment to demonstrate the benefit of the active study treatment vs. Placebo for achieving and maintaining clinical remission. **Proposed change:** Delete reference to steroid taper during induction.Mandatory steroid tapers during induction periods of short duration introduce the potential for provoking severe flares in patient who are already ill. Please allow sponsors the ability to keep steroids stable during induction studies. It is understood that labelling would reflect the study design. This sentence adds to the confusion about whether steroid-free remission is an expected primary endpoint or there is the option for it to be a secondary endpoint.Here the document again suggests that the primary endpoint should be steroid-free remission, which is inconsistent with some earlier statements in the document and it is not clear which co-primary endoscopic endpoint is acceptable. |  |
| 286-292 |  | In active comparator studies with a placebo, please clarify which comparison is expected to support approval—versus placebo? Or the active comparator? |  |
| 318-319 |  | Formal comparisons to active comparators are logistically not very feasible in a pivotal trial exploring various dose regimens as well as a placebo for proper safety evaluation; thus should not be a requirement for regulatory approval; informal “reference” arms with an active comparator are prone to alfa and beta errors and may rather cause confusion, unless strong superiority is expected for the IMP and should not be requested.Add-on of IMPs to TNF inhibitors may be difficult to justify ethically due to safety concerns and would not allow proper safety evaluation for compounds with improved safety profile over TNF antagonists |  |
| 324-326 |  | **Comment:** In maintenance of remission trials, recommend that patient who are presently on the test drug should be re-randomized to continue the test drug or switch to placebo. These are patients who were failing their standard of care drugs and thus entered the trial; were induced, went into remission, and now are entering the maintenance phase. Is it ethical to re-randomize these patients to placebo in a waxing-waning chronic disease that is never cured without colectomy and that is known to recur off medication? |  |
| 335 |  | **Comment:** The guidance states that “Patients who are steroid free remission (as defined above) are eligible for inclusion into the trials". As indicated in the response to line 284 of the guidance above, we have concern regarding the tapering of steroids during a 6-8 week induction study & therefore, this concern carries over to the definition of the target population for maintenance studies. We advocate for the target population of a maintenance study to include patients who achieve a pre-specified measure of clinical response as this represents the broadest population of patients to be treated in the clinical setting. Among these patients will be those achieving clinical remission both on and off steroids who can then be the target populations for major secondary analyses for maintenance of clinical remission and steroid-free remission with appropriate statistical controls.**Proposed change:** Acknowledge that patients in clinical response are an appropriate primary target population for the assessment of maintenance therapy. |  |
| 335-339 |  | Requirement for inclusion into maintenance trials of only patients who are steroid-free is problematic, as 8-12 week induction trials may not be sufficient in duration to wean all subjects completely off steroids. Furthermore, continuation of treatment in patients only who have reached a stringent endpoint of remission, steroid discontinuation AND mucosal healing is not consistent with the clinical paradigm of treating patients with at least a partial PRO and/or endoscopic response to induction treatment. This requirement will also have a large impact on the side of induction trials needed in order to identify adequate numbers of subjects for maintenance trials.  |  |
| 335, 340 |  | **Comment:** Only patients who are in steroid-free remission are eligible for inclusion into the maintenance phase. This is not a technically achievable outcome at the end of induction, as patients who enter the induction period on corticosteroids will most likely remain on steroids for the duration of this period and have protocolized weaning when they enter maintenance. Only patients in remission should enter maintenance. This is highly restrictive and would result in unfeasibly large induction studies. Including patients with a clinical response into maintenance studies reflects real-world clinical practice and allows sponsors to address important, clinically relevant questions, such as determining the proportion of responders who enter remission.Sponsors should also be encouraged to allow non-responders to continue on active medication in limited circumstances where the sponsor predicts that subjects are likely to have a “late response” to the study drug, e.g. Ustekinumab’s UNITI phase 3 studies in Crohn’s disease.A proposal is to allow patients with symptomatic response to be included in the maintenance study with a stratification factor of remitter and responders. The primary endpoint of this maintenance study would be based on both responders and remitters. Subgroup analyses would be provided to show consistency between subgroups.**Proposed change (if any):** Consider changing these lines to reflect that patients in clinical response should be allowed to enter maintenance studies. |  |
| 340-353 |  | **Comment:** Also refer to comments in response to Lines 136-141.The notion that true maintenance of efficacy can only be demonstrated in the context of a randomized-withdrawal study (vs. placebo) or only among induction responders/remitters is concerning. As discussed in an earlier section, the arbitrary designation of induction and maintenance study periods limits one’s ability to evaluate the true efficacy potential of a MOA; and is highly inconsistent vs. clinical practice.The maintenance of efficacy among “induction responders” only provides insights into the continued benefit observed among patients who achieved an initial response/remission within an arbitrarily set “early” timeframe, but ignores the rest of the population treated. Whereas, the holistic approach under a treat-through study design, will support the evaluation of long-term efficacy at a population level, including both early and late responders to initial (induction) treatment and their response to continued long-term treatment (maintenance), and will also support the desired “maintenance of remission among induction remitters” analysis.In addition, evaluation of endoscopic/ histologic endpoints would be significantly challenged in the setting of a randomized-withdrawal (to placebo) study, since the kinetics of disease worsening (upon discontinuation of treatment) by these outcomes measures are unknown. A treat-through study design is much more favourable and preferred for the evaluation of these important outcomes.It should be noted that comparison to standard of care comparators (e.g. anti-TNF) using this methodology incurs substantial complexity. We believe comparison to SOC in both induction and in maintenance phases of treatment as part of the confirmation study is best accomplished using a treat through methodology.Finally, the validity or requirement of a randomized withdrawal (to placebo) design to demonstrate the need for maintenance treatment in patients with UC should be questioned. After 20 years and numerous trials across different MOAs, there is no evidence that patients with UC can be successfully managed without active maintenance treatment. All of the randomized withdrawal studies of biologic agents have demonstrated the need for continued maintenance treatment. It should also be noted that randomized withdrawal placebo studies are inconsistent with clinical practice and is a design feature that is a significant deterrent to patient recruitment.  |  |
| 355-356 |  | **Comment:**  The guidance recommends that the primary endpoint of maintenance studies should be steroid-free remission maintained without surgery. In clinical trials colectomy is considered one of potentially several possible treatment failures in the analysis of efficacy; therefore study patients who achieve or maintain remission at the end of study have not undergone colectomy. Further, pursuant to comments related to line 335 above, we believe that clinical remission among subjects induced into clinical response represents the broadest evaluation of maintenance therapy and should be the primary endpoint of a maintenance study. Pre-specified major secondary endpoints of maintenance of clinical remission and steroid-free remission based on appropriate subgroups would provide additional important measures of the effectiveness of a maintenance therapy.Furthermore there has been a generally low incidence in some UC populations, including an unselected UC population in Europe (Hoie O, eta l (2007) Gastroenterology 132:507-515) as well as what was observed in the ACT studies of infliximab (Sandborn WJ (2009) Gastroenterology. 137:1250-1260) that the incidence of surgery is relatively low of a 1 year period. Therefore, it would be a challenge to power a clinical study for a steroid free remission endpoint that includes the absence of surgery. **Proposed change:** Update recommendation on the primary endpoint to clinical remission among subjects responding to induction treatment with major secondaries focused on the subgroups of subjects who maintain clinical remission or achieve steroid-free remission during maintenance therapy. |  |
| 355 |  | Different primary EP then recommended before (lines 175, 284); also the 1yr-surgery rate is too low to see a significant reduction in a typical trial population and setting |  |
| 370-372 |  | Please provide guidance how a maintenance trial is to be done for comparators that are indicated only to be continued in induction responders (i.e., anti-TNF agents). Parallel group designs are problematic in that, per label, patients without response to the anti-TNF agent (or integrin inhibitor) are not to continue the drug. This could lead to differential drop outs between arms that, as the document has already indicated, are methodologically problematic. On the other hand, it seems inappropriate to take patients who responded to one drug and randomize them to a different agent for the purposes of testing “maintenance.” Much more guidance is needed here, as sponsors are really struggling with these questions.  |  |
| 371-372 |  | Unclear how an AC should be incorporated in a randomized withdrawal design; that would require to switch e.g. TNF-refractory pts responding to induction with the experimental drug to TNF or a different drug of unknown activity for that patient. Ethically very difficult and not acceptable to many investigators and patients. |  |
| 382-392 |  | The discussion of refractoriness in to other drugs in a maintenance setting is unclear. Is this section intended to refer to the concomitant/prior meds prior to induction with whatever agent was used prior to putting the subjects into a maintenance trial? |  |
| 395-396 |  | **Comment:** Please clarify if the one year maintenance phase can include 12 weeks of steroid tapering at the beginning of the maintenance phase.We consider 6 months as appropriate as one year for steroid-free remission, and therefore recommend that patients must be steroid free for 6 months prior to the one year primary endpoint assessment. We propose to allow a single, short-term steroid dose due to other, unrelated conditions. |  |
| 431 – 433 |  | **Comment:** As the draft guideline states, UC is rare below 10 years of age. Yet the clinical development is asked to include patients from 2 years of age. Fully-powered clinical efficacy studies in the paediatric population 2 – 10 years of age might not be feasible due to the low patient numbers. Therefore clarification is needed on what is expected to be demonstrated in those children. (see also next comment) |  |
| 431-437 |  | **Comment:** The comment that children from 2 years of age and older should be included in clinical development programs requires clarification. The key point here is the age at which the subject’s IBD was diagnosed, which is inversely proportional to the likelihood that the subject has a rare, monogenic cause for IBD. We would advocate that the age at diagnosis of patients that should be included in pediatric IBD clinical trials is 7 and above, which is consistent with the current definition of “Very Early Onset IBD” (VEOIBD, patients with IBD onset <6 years of age). Furthermore, even though the draft guidance discusses testing for monogenic defects that may cause IBD, it states that subjects can be included or excluded based on the defect. This guidance is confusing, as it appears to be mandating the inclusion of pediatric subjects with rare, monogenic causes for IBD, in pediatric clinical trials that are designed to investigate idiopathic IBD. **Proposed change (if any):** 1) Consider rewording this section to base the pediatric subject’s age on the age at diagnosis, rather than the current age of the subject.2) Consider explicitly using the term “Very Early Onset IBD” to make it clear that the intention of this guidance is not to mandate the inclusion of pediatric subjects with rare, monogenic causes of IBD in trials designed to include subjects with idiopathic IBD. The Agency should consider communicating a clear expectation that rare, monogenic causes of IBD will be considered orphan diseases.  |  |
| 436-437 |  | **Comment:** Please clarify the term “younger children” by adding an age.We agree to genetically testing children, but should not be the sponsor´s burden.**Proposed change (if any):** “Younger children **<6 years of age** **~~should be~~****should have been** genetically tested for known immunological defects and in-or excluded depending on the defect.” |  |
| 443-463 |  | In designing clinical trials, extrapolation (particularly for conclusions of efficacy) implies that the adult trial leads the paediatric trial. Only then can extrapolation result in a reduction in the amount of data required. While the goal has been to have a concurrent adult/paediatric development, this benefits a staggered development more than the latter. If a concurrent development is pursued (at least with adolescents), the concept of extrapolation, even if it is conceivable (say, same pharmacological class), seems to be not helpful. **Proposed change (if any):** the guidance should explain how extrapolation, where conceivably applicable, can be used in concurrent development; endpoints for adults and paediatrics are not the same e.g. PUCUI; time points of assessments are not the same  |  |
| 488-489, 492-493 |  | Repeated endoscopies in children are problematic. Children in particular have more issues with the preparatory regimens than adults do, as these and the procedure itself interfere with school and activities. Please consider allowing a symptom related endpoint (PUCAI) at least for induction endpoints (i.e., select either induction or maintenance where endoscopy is required but not both). Paediatric UC, as an orphan disease, is already difficult to enrol into clinical studies due to the rarity of the disease. Multiple invasive procedures deter enrolment into clinical studies.  |  |
| 490-491 |  | **Comment:** Please clarify, if clinical response/remission alone could be an acceptable primary endpoint for induction, if combined with endoscopic MH for maintenance? This would allow for having fewer endoscopies in children.For trials with both an induction and maintenance phase, is it acceptable to perform endoscopy at the end of the maintenance phase and not at the end of induction? Would it be acceptable to separate endoscopy from the induction/maintenance paradigm (i.e. perform endoscopy at the 6 month time point)?Or Please clarify, if endoscopy has been shown in adults, can it be waived in children?Please clarify the circumstances when it is acceptable to waive endoscopy within a trial? Can endoscopy be waived in certain age groups (i.e. under 12 years of age)? |  |
| 504-519 |  | When extrapolation is not possible, a non-inferiority trial cannot be operationalized in terms of the choice of the non-inferiority margin.**Proposed change (if any):** explain whether the margin can be based on the adult trials (from which extrapolation cannot be used) or other paediatric trial in the same indication. |  |
| 505 |  | **Comment:** Please consider the current joint ESPGHAN/ECCO/PIBDnet/Canadian Children IBD Network position statement on placebos in pediatric IBD clinical trials. Turner *et al. J Ped Gastroenterol Nutr* 2016. Pediatricians will only support the use of placebos in pediatric IBD studies where there is genuine equipoise between active treatment and placebo.**Proposed change (if any):** The paragraph on placebos in pediatric studies may have to be re-written to reflect current expert guidance.  |  |
| 515-516 |  | **Comment:** Please clarify, what is the risk of “lack of efficacy”?**Proposed change (if any):**“In case the use of placebo control group is considered necessary, **where there is no data from adults,** all efforts need to be made to assure that the patient is not exposed to more than minimal risk”. |  |
| 520-521 |  | **Comment:** The guidance states that in pediatric trials, combined induction and maintenance trials can be accepted (as opposed to what was stated for trials in adults). Are these combined trials in children allowed without re-randomization to continued study drug vs. withdrawal to placebo in the maintenance phase? Please provide further guidance. |  |
| 536-538 |  | **Comment:** Not all mechanisms of action for the treatment of Ulcerative Colitis may impact adaptive immunity. If preclinical data exist demonstrating that vaccination responses are not affected this should suffice. We suggest removing the requirement that studies evaluate impact on vaccination of all drugs with new mechanism of action, and limit to drugs interfering with adaptive immune response only where preclinical data suggest increased risk of failed vaccination. |  |
| 542-543 |  | **Comment:** Please clarify “ if a cross company registry” or a “cross paediatric GI registry established by a professional organisation such as ECCO” is intended |  |
| Sections 8.3.1.1 – 8.3.1.5 |  | **Comment:** Further clarification on whether these sections apply to above 10 years old patients’ needs to be provided. Older adolescents (14 and older) could be included in the adult development studies. If the sections apply to 2 – 10 year olds (as understood per introductory statements to Section 8.3.1), such studies may face feasibility issues. |  |

Please add more rows if needed.

1. Specific comments on text – Minor Comments

| 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)* |
| --- | --- | --- | --- |
| 11 |  | **Comment:** Suggest to add ‘ulcerative colitis’ |  |
| 32 |  | There is in reference to “Pharmacodynamics” as section 7.1.2 in the Table of Contents but there is no text/information in the document regarding this topic in section 7, where 7.1.2 describes the topic “Interactions” |  |
| 107 |  | **Comment:** “includes pancolitis”. E3 distribution, involving the colon proximal to the splenic flexure is pancolitis, by definition. See Satsangi *et al. Gut* 2006 55(6): 749-53.**Proposed change (if any):** Delete “includes” |  |
| 182-183 |  | Please describe how “standardization of reading should be convincingly demonstrated” can be demonstrated (what is expected?)  |  |
| 201-202 vs 204 |  | **Comment:** Please define “histological normalisation”.What is the difference between “histological normalisation” and “histological remission”? We suggest to use the same terminology. |  |
| 211 |  | **Comment:** Please clarify how steroid sparing effect is different from the primary endpoint. |  |
| 260-262 |  | **Comment:** Appropriate follow-up period off therapy is recommended to see if patients who are in remission at the end of treatment remain in remission at the end of follow-up. However, with the exception of corticosteroids, there is no medication for UC that is withdrawn (unless there is an adverse event) even when the patient is in remission. This is a chronic waxing and waning disease, and there is ample evidence that withdrawal of maintenance medication results in an increased risk of relapse and greater difficulty in re-inducing remission. In addition, with certain biologics, withdrawal of therapy and restarting may increase the risk of developing antibodies to the drug and reduce its effectiveness. |  |
| 262-264 |  | **Comment:** “Patients on steroids at entry should have their dose tapered according to predefined tapering schedules. Obtaining steroid-free remission should be the goal of therapy.”**Proposed change (if any):** Consider carefully distinguishing between corticosteroid-free remission as a well-established goal of therapy in clinical practice and corticosteroid-free remission as an endpoint in clinical trials. The above sentences may lead to confusion in this regard. |  |
| 280-281 |  | As patients who are newly diagnosed may be appropriate for inclusion in studies (i.e. Bionaive patients), we do not believe a 3 month period from diagnosis is appropriate. We suggest considering a provision of 3 months of symptoms prior to diagnosis in newly identified patients.  |  |
| 325 |  | **Comment:** “Patients who are presently on the test drug should be randomised to continuing the test drug or switching to …”It seems clear from the chapter 7.2.2.2.2 below that re-randomisation is what is meant in this sentence**Proposed change (if any):** Patients who are presently on the test drug should be re-randomised to continuing the test drug or switching to … |  |
| 340-346 |  | **Comment:** text on lines 340 -346Trials combining induction treatment and maintenance treatment should preferably only enter patients that have achieved remission (in either the trial drug or comparator group), into the maintenance phase. Responders may be included in the maintenance phase as it is considered relevant to study if continued treatment in responders may eventually lead to remission. However, if the intended claim is “maintenance of remission”, the primary analysis should be based on the remitters only.**Proposed change (if any):**Trials combining induction treatment and maintenance treatment should preferably only enter patients that have achieved remission (in either the trial drug or comparator group), into the maintenance phase. Responders may be included in the maintenance phase as it is considered relevant to study if continued treatment in responders may eventually lead to remission *or if maintenance of response is an intended claim*. However, if the intended claim is “maintenance of remission”, the primary analysis should be based on the remitters only. |  |
| 393-394 |  | The tapering schedule given should specify the pertinent group of steroids. As commented earlier, there are different groups/compounds which may require different schedules. |  |
| 400-401 |  | **Comment:** For the reasons that the author alludes to on lines 398-400, topical rectally administered therapies are usually excluded from industry-sponsored clinical trials in UC. Given this fact, the statement on lines 400-401 is confusing.**Proposed change (if any):** The sentence on lines 400-401 should be amended or removed. Clarification is required.  |  |
| 402 |  | Comment**: Treatment with antibiotics should be at the discretion** of the sponsor.**Proposed change (if any):** “Antibiotics should normally be excluded **and at the discretion of the sponsor** and in severe disease, anti- cholinergic, anti-diarrhoeal, NSAID and opioid drugs should not be allowed as they may contribute to worsening of the relapse”. |  |
| 402-404 |  | It is infeasible to exclude antidiarrheal and pain medications in a 52 week study in this patient population. Exclusion of these medications will greatly limit enrolment and limit generalizability of studies in patients with UC |  |
| 422 |  | **Comment:** “Furthermore, it is important to get information on re-treatment outcomes even after a longer time interval without treatment with a specific drug.”Given this information may take long time to collect, it should not be a requirement for the initial submission. Please specify whether this information can be provided post marketing**Proposed change (if any):** Furthermore, it is important to get information on re-treatment outcomes even after a longer time interval without treatment with a specific drug, **this should be considered as part of post marketing commitment** |  |
| 431  |  | **Comment:** Please clarify that paediatric Ulcerative Colitis is a rare disease in younger children. **Proposed change (if any):** “**Paediatric** UCis **a** rare **disease and younger ~~in~~ children (i.e. under 4)** ~~below 10 years of age~~ may develop a different disease phenotype compared with adolescents or adults.” |  |
| 488 |  | **Comment:** Please clarify that clinical remission is the same for both adults and children. |  |
| 488-489 |  | **Comment:** Please clarify that clinical remission and endoscopic MH could be separated in time. How do you re-randomize, based on the co-primary endpoint? Can you re-randomize based on response? |  |
| 492-493 |  | **Comment:** Please clarify thatendoscopy can be performed within a subset of patients.  |  |
| 495-496  |  | **Comment:** In a paediatric UC population, the revised guideline proposes use of the PUCAI as a surrogate for symptomatic remission. However, there are two versions of the PUCAI – one which is self-reported by the patients (PRO) and another which is reported by the physician/investigator (ClinRO). Guidelines from ISPOR (Matza et al., Value in Health 16 (2013) 461 – 479) suggest that reliability of responses to a PRO cannot be assumed before the age of 8 (assuming no cognitive functioning deficits). Given that the agency proposes that “the clinical development program should include children from 2 years of age and older”, does the agency have any advice on when to utilise the PRO and the ClinRO version of the PUCAI?**Proposed change (if any):** clarify which version of the PUCAI EMA recommends for paediatric studies |  |
| 498-499, 500-503 |  | “Sustained relapse-free steroid-free remission” is a stringent endpoint (more stringent even than the endpoint advocated for adults” and may discount benefit in subjects who achieve remission but are not entirely able to discontinue steroids or who suffer a brief relapse but subsequently improve. It is acknowledged that steroid-free remission is an appropriate endpoint for a given patient, it is potentially overly stringent for a clinical trial endpoint, especially in a heavily treatment refractory population with a large unmet need.  |  |
| 510-514 |  | The acknowledgement regarding the limitations of placebo use in paediatric UC patients is appreciated. However, the suggestion that a NI study against an active comparator are reasonable replacements runs counter to the concept of extrapolation (whereby similar of effect in paediatric subjects needs to be demonstrated in a drug that has already proven efficacy and safety in adults) and are infeasible due to the need for relatively large samples sizes (in an orphan disease) and the potential need for a double-dummy design (in the case of differing routes of administration between study drugs).  |  |
| 530-532 |  | **Comment:** Please specify “development”. We propose to change the wording to “growth velocity”**Proposed change (if any):** “Post-study/post authorisation long-term data, either while patients are on chronic therapy or during the post-therapy period, are necessary to determine possible effects on **~~maturation and development~~** **growth velocity**”. |  |
| 530-532 |  | Does this need for long-term safety data in growing children mandate the need for post-approval registries? |  |
| 543 |  | If registries are established and are disease (and not drug) based, does each company with a new drug have to establish such a disease-based registry or can they collaborate and form a single disease-based registry with patients on multiple drug regimens? |  |