28 June 2018
EMA/CHMP/354664/2017
Gastroenterology Drafting Group (GDG)

# Overview of comments received on ''Draft guideline on the development of new medicinal products for the treatment of Ulcerative Colitis' (EMA/CHMP/EWP/18463/2006 Rev. 1)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

| Stakeholder no. | Name of organisation or individual |
|---|---|
| 1 | Celgene |
| 2 | Tillotts Pharma AG |
| 3 | The British Society of Gastroenterology (BSG IBD) |
| 4 | EFPIA |
| 5 | Gilead Sciences International Ltd |
| 6 | Medicines Evaluation Board |
| 7 | ECCO |
| 8 | Takeda Development Centre Europe Limited, United Kingdom<br>Takeda Pharmaceuticals Inc., United States |

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# 1. General comments – overview

| Stakeholder no. | General comment (if any) | Outcome (if applicable) |
|---|---|---|
| 1 | The update of the Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis is an important revision which provides further details of study design both in adult and paediatric patients. Celgene welcomes the opportunity to review this draft.<br><br>It is important that the EMA guideline on ulcerative colitis and the FDA guidance on ulcerative colitis remain consistent in their simultaneous revisions.<br><br>Several references to remission and mucosal healing are made throughout the guideline interchangeably. There should be clarity in terms of definitions that are used throughout the document (see specific comment on line 194 below). | Remission encompasses both mucosal healing and symptomatic remission. This has been clarified. |
| 3 | Section 4.1.4 UC in remission. The definition of remission in UC should also be clinical and endoscopic rather than endoscopic with no or very mild symptoms. Page 5 line 125. | Please refer to responses given below |
| 3 | Section 6.1.1.2 Secondary endpoints. It is proposed that mild to moderate and moderate to severe UC have separate trials, but it should also be acknowledged that the definitions of mild and moderate are weak and poorly replicated. Page 7 line 217. | Please refer to responses given below |
| 3 | Section 7.2.1 Study design – Dose finding studies. The proposed duration of phase 2 dose finding studies at 6 -8 weeks is probably too short. 8 to 12 weeks would be more appropriate particularly if endoscopic and histological changes are assessed. Page 7 line 241 | Please refer to responses given below |
| 3 | Section 7.2.2.1.1 Confirmatory studies, Active disease, Design | Please refer to responses given below |

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| | elements. As with Crohn's disease most studies currently maintain steroid dosage at entry dose until the primary endpoint of active disease. This may be a prolonged steroid treatment period but is designed to avoid the interference in therapeutic signal related to steroid withdrawal. Steroid withdrawal is usually done early in the maintenance study. The proposal here is a significant change. If steroids are tapered and withdrawn during the induction study fewer patients will show response and with more variables it may be more difficult to interpret the results. page 8 line 262 and page 11 line 393 | |
| 3 | Section 7.2.2.1.2 Patient selection. Page 8 line 280 suggests a minimum time from diagnosis to trial of 3 months, but page 9 line 299 refers to First line treatment, these statements are not compatible, the 3 months criterion should probably be removed. | Please refer to responses given below |
| 3 | Section 7.2.2.1.3 Choice of endpoints. Primary endpoints for active disease (page 9 line 284) should be clinical and endoscopic remission, not steroid free remission which is more appropriate for maintenance studies. This also relates to point 4 above. If confirmatory studies are to be done with steroid withdrawal in the induction phase then steroid free clinical and endoscopic remission could be the primary endpoint, but it will be achieved in a small minority of patients. | Please refer to responses given below |
| 4 | 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 | Not agreed. Please refer to responses given below |

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| | 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. | |
| 4 | 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".<br>1. 'Maintenance of remission/Prevention of relapse': primary endpoint of "**maintenance of corticosteroid-free remission without surgery throughout at least 12 months**"<br>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.<br>2. **Co-primary endpoints**<br>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 | 1. Agreed. The text has been revised to remove this requirement.<br>2. The request for co-primary endpoints are maintained.<br>3. Agreed. Inclusion of responders is allowed in maintenance studies.<br>Please refer to responses given below |

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| | assessment of signs and symptoms and endoscopic improvement is proposed.<br><br>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.<br>**3. Design of maintenance trial**<br>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. | |
| 4 | 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. | No changes necessary |
| 4 | Comments: 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 | Not accepted, the age range sould be coveed from 2 years above, especially in drugs with new mechanism of action |

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| | 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. | |
| 4 | 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". | This is a general issue and fall outside the scope of this guideline |
| 6 | Lines 136-141:<br>It is recommended to evaluate induction of remission and maintenance of remission in separate studies.<br>In line with this, it is proposed to remove lines 340-349 (see textual comments below).<br><br><u>Motivation</u>:<br>Proposed text with respect to treatment of active disease/induction of remission and treatment for maintenance of remission/prevention of relapse is unclear. 'Treat through' studies to evaluate maintenance of remission are not favourable, as disease activity and likely also the need for medicinal treatment will be lower compared to more active disease. Because of this, though potency of study treatment itself is the same, it may be more difficult to demonstrate differences in treatment effects between implemented study treatments during maintenance treatment compared to induction treatment. Hence, 'treat through' studies may not be adequately powered to observe clinically significant and clinically relevant differences between study treatments during both induction of remission and maintenance of remission. In addition, in a 'treat through' study, study medication and/or concomitant medication may unintentionally be provided to | Please refer to responses given below |

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| | patients in remission. Therefore, a 'treat through' study design might hamper assessment of the maintenance of remission and might consequently complicate the acceptance of this part of the indication. Partly because of aforementioned concerns with respect to a 'treat through' design, conditions in which study treatment may be provided to patients in clinical remission should be standardized for clarity and to avoid misinterpretation. For above reasons, it is recommended to evaluate induction of remission and maintenance of remission in separate studies.<br><br>In addition, the recommendation for the conduction of separate induction and maintenance studies is also in line with proposed sections on treatment of active disease/induction of remission (section 7.2.2.1.) and maintenance of remission/prevention of relapse (section 7.2.2.2.).<br><br>In line with the above, it is proposed to remove lines 340-349. | |
| 6 | Section 6.1.1.1. Primary endpoint<br><br>It is agreed that symptomatic remission and endoscopic remission (i.e. mucosal healing) concern co-primary endpoints for both induction and maintenance treatment.<br>Important secondary endpoints for these treatment phases concern the proportions of patients in whom either or both of these co-primary endpoints are achieved without steroids. Further, (reduction in) corticosteroid dose should be specified.<br><br><u>Motivation</u>:<br>On the one hand, achieving/maintaining remission free of steroids is considered primary endpoint (line 173) in proposed guideline. On the | Please refer to responses given below |

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| | other hand, symptomatic remission and mucosal healing irrespective of steroid use are considered co-primary endpoints (line 188). Hence, definitions of (co-)primary endpoints need to be specified more clearly for appropriate implementation in clinical studies (see textual comment below).<br><br>According to the international STRIDE consensus committee of experts in inflammatory bowel disease treatment of ulcerative colitis should be targeted to achieve remission of clinical signs and symptoms (i.e. resolution of rectal bleeding and diarrhoea/altered bowel habit) AND endoscopic remission (defined as a Mayo endoscopic subscore 0-1)(Peyrin-Biroulet et al. 2015). This is in line with current definition of ulcerative colitis in remission of the European Crohn's and Colitis Organization (ECCO)(Dignass et al. 2012). Based on this consensus, it is agreed to define both symptomatic remission and mucosal healing as co-primary endpoint in proposed guideline. In this way it is avoided that efficacy is demonstrated for a combined primary endpoint, while efficacy with respect to either co-primary endpoint is not demonstrated.<br><br>As it is aimed to achieve/maintain remission without steroids, important secondary endpoints for both induction and maintenance treatment concern the proportions of patients in whom either or both of the co-primary endpoints are achieved either without or at particular dose(s) (reductions) of steroids. | |
| 6 | Section 7.1 Pharmacology studies<br><br>Pharmacodynamic effects in addition to pharmacokinetics and interactions are important with respect to treatment pharmacology in ulcerative colitis (Quetglas et al. 2015). It should therefore be | There are no generally accepted pharmacodynamics parameters for this disease. Thus no guidance can be provided. |

| Stakeholder no. | General comment (if any) | Outcome (if applicable) |
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| | considered to provide some guidance with respect to the evaluation of pharmacodynamic effects (e.g. extent of metabolic conversion) in clinical studies. | |
| 6 | Section 8 Safety<br><br>As in the current EMA guideline on ulcerative colitis, it is recommended to include a statement in the safety section that consideration should be given to potential interference/contribution of concomitant therapy. This is because treatment interactions may alter clinical effects of study treatment. | This is general and not specific for this guideline. Thus it should not be included. |
| 6 | Section 8.3.1. Studies in paediatric patients<br><br>It is recommended to evaluate effects of a new medicinal product for ulcerative colitis first in adult patients. Provided both efficacy and safety of this medicinal product are acceptable in adult patients, a paediatric study with a limited number of study patients (e.g. 30-50) should be conducted. Such a study has two major purposes:<br>- confirmation of observed effects for adults in a paediatric patient population<br>- demonstration of no evidence of effects of proposed medicinal product with respect to growth and maturation. Observation period should be sufficiently long for this evaluation.<br>For evaluation of effects on growth, an observation period of 2 years is recommended. Observation time with respect to maturation will vary depending on the age at inclusion and should therefore be justified by the applicant.<br>A statement about the above should be included in revised guideline. | Accepted |
| 6 | Motivation:<br>Some reviews indicate that impaired growth and sexual maturation | Accepted in previous comment above |

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| | may occur in paediatric patients with ulcerative colitis (Malmborg & Hildebrand 2016; Kapoor et al. 2016). By contrast, in a review by Fumery et al. (2016; 26 studies), patients with paediatric-onset ulcerative colitis did not appear to have any significant growth retardation or delayed puberty. Because of these contradictory findings, no definite conclusions can be drawn with respect to the impact of ulcerative colitis (and its treatment) on growth and maturation. Anyhow, aforementioned potential risks with respect to impaired growth, and sexual maturation are not applicable (or at least much less likely) in adult compared to paediatric patients with ulcerative colitis. Because of this, it is recommended to evaluate effects of new medication in adult patients first.<br><br>Provided both efficacy and safety of this medicinal product are acceptable in adult patients, a paediatric confirmatory study with a limited number of study patients (e.g. 30) should be conducted in order to (1) confirm observed effects for adults in a paediatric patient population, and to (2) evaluate potential effects of proposed medicinal product with respect to growth and maturation. Observation period should be sufficiently long to detect differences between study treatments with respect to these latter endpoints (Malmborg & Hildebrand 2016). Based on this and common recommendations with respect to studies evaluating growth (e.g. EMA/CHMP/SAWP/646541/2016), an observation period of 2 years is recommended for the evaluation of effects on growth. Observation time with respect to maturation will vary depending on the age at inclusion. This is because maturation peaks at pubertal age, but is more limited at younger age. Hence, observation time with respect to maturation should be justified by the applicant. | |

| Stakeholder no. | General comment (if any) | Outcome (if applicable) |
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| | A statement about the above should be included in revised guideline. | |
| 7 | The European Crohn's and Colitis Organisation's (ECCO) main mission is to improve the care of 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 current "Guideline on the development of medicinal products for the treatment of Ulcerative colitis (CHMP/EWP/18463/2006)" would be worthy of support and collaboration. Because of this and in view of a mutual advantage of a future growing collaboration, ECCO is extremely motivated to provide pertinent observation at this stage. | No changes necessary |
| 8 | In 2017, anti-TNF and anti integrin biologic agents are routinely used for moderate to severe Ulcerative Colitis. Furthermore, in the last decade we are observing a significant rise in outpatient starts for biologics. Previously, majority of patients with UC on anti-TNF were hospitalized before the biologic was offered. Thus, clinicians are currently recognizing steroid dependence and prescribing biologics in cases where patients are either non-responsive or intolerant to immunosuppressive drugs like AZA and 6MP. Disease severity also contributes to the decision for early biologic use. More extensive the disease increases the likelihood of early biologic use. The section 4.1.3 could be modified to represent patient sub-groups based on treatment exposure. These would facilitate development of new medicines for Ulcerative Colitis. After the end of line 124 the following could be included.<br>1. Steroid refractory disease- these patients have failed recommended dose (amount as well as duration) and are continuing to flare. These patients can be Bio-Naive or Bio-experienced | General recommendations in terms of defining refractory/dependent patients based on previous treatment experience has been given. It is outside the scope of this guideline to provide detailed definitions on all possible situations. |

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| | depending on their treatment history.<br><br>2. Anti TNF refractory – there are 3 approved anti TNF agents and patients that have failed 2 of the 3 agents are considered refractory. Anti-TNF therapy in UC is slightly less effective than in CD.<br><br>3. Anti-integrin refractory- these cases have failed anti-integrin and are in need for an alternative treatment approach.<br><br>4. UC refractory to biologic therapy- these patients have been exposed to more than one class of biologics and have failed induction and or maintenance of remission. They are in need of novel medical therapies. | |

## 2. Specific comments on text

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| 194 | 1 | Comment: There is currently no literature or data showing precedence of the requirement to meet both mucosal healing and symptomatic remission in patients as a secondary endpoint. It is not well understood how this would operate in clinical trials and is expected to be a high bar. This requirement would be best suited to exploratory studies.<br><br>Proposed change (if any): 'Secondary endpoints<br>~~**Patients achieving both MH and symptomatic remission'**~~ | Not accepted. Each part of the endpoint (achieving both objective (mucosal healing) and subjective (symptomatic) control) are clinically highly relevant. This secondary endpoint aims at defining how many patients achieve both of these endpoints. |
| 340-344 | 1 | Comments: Celgene would like to suggest that the primary endpoint for a maintenance study be based on the full population of patients who are included into the study as either responders and remitters and that a supportive subgroup analysis be based on remitters only. This would be consistent with the clinical practice where patients in clinical response will continue on the effective therapy and allows an assessment of the benefit/risk ratio in the population most likely to receive treatment in clinical practice. It would also provide an assessment of the effect of longer term treatment on achieving clinical remission in those initially with clinical response. It would allow for efficient recruitment of patients into the maintenance study since it is expected fewer patients will achieve remission than response in induction.<br><br>Proposed change (if any): 'Trials combining induction treatment | Partly accepted. The section has been revised. The revised guideline allows development programs that aim at a more general indication instead of the previously recommended strictly separate indications of induction and maintenance of remission. For the more general indication, the full population (responders and remitters) may be used for the primary efficacy analysis. However, if a classical "maintenance of remission" indication is sought, the primary efficacy analysis should only include remitters (as you cannot maintain something that is not achieved in the first instance) |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| | | and maintenance treatment should preferably only enter patients that have achieved remission (in either the trial drug or comparator group), into the maintenance phase. Inclusion of responders is acceptable as it may yield important information on the potential benefit of continued treatment in this population. ~~**However, i**~~ **I**f the intended claim is "maintenance of remission", the primary **endpoint should be based on the full population of patients who are included into the study as either responders and remitters, and a supportive subgroup** analysis should be based on remitters only.' | |
| 425 | 1 | Comment: Celgene would suggest to use the same section header as for the EMA draft guideline on the development of new medicinal products for the treatment of Crohn's Disease.<br><br>Proposed change (if any): '8.3.1. ~~**Studies in p**~~ **P**aediatric patients' | Accepted |
| 438-439 | 1 | Comment: Celgene would welcome a clarification on whether 'adolescents' in that sense is defined according to ICH E11 2.5.5. (i.e. 12 to 16-18 years [dependent on region]). This would support global clinical development. In case it is not, we would appreciate a clarification of the age range for adolescents to be included into trials with adults. | No need of clarification on paediatric age definitions: Adolescent age is well defined.<br><br>**Age definition is mentioned in ICH E11, but the cut of age for patients to be included into the adults studie shoul still be justified by the applicant, depending on the products profile** |
| 473-476 | 1 | Comments: Celgene would like to ask for clarification on the following sentence and to suggest the below rewording.<br><br>Proposed change (if any): 'The results of this covariate analysis can be used in case a certain exposure (AUC or Ctrough) for instance similar to adults is aimed for, to identify whether~~,~~ | Partly accepted |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| | | different mg/kg doses per age group **are ~~may be~~** needed **~~to define~~** to reach the same exposure **obtained in adults ~~across the entire paediatric age range~~**, given the fact that the PK may change in a non-linear manner with weight.' | |
| 57 | 2 | Comments: UC affects both rectum and colon.<br><br>Proposed change (if any): UC is a chronic, relapsing inflammatory bowel disease affecting the rectum and colon | Accepted |
| 103 | 2 | Comments: Please specify what infectious diseases need to be excluded.<br><br>Proposed change (if any): List the most important infections to be tested. | Not accepted. Exclusion of infectious causes is general clinically knowledge and depends on the setting. This section is not intended to be a full textbook of UC. |
| 109 | 2 | Comments: Define disease activity and severity – in the text they are used somewhat as interchangable. | Not accepted. As stated severity describes the grade of disease activity. |
| 131-132<br>140-141 | 2 | Comments: Information in lines 131-132 and 140-141 could be interpreted as contradictory.<br>A restructuring of section 5 may increase comprehensibility.<br>Lines 131-132 describe the general requirement to study induction and maintenance. Lines 133-135 describe the exceptional case where both indications are not feasible (therefore induction or maintenance have to be studied) and lines 136-141 are then dealing again with the general case where induction and maintenance studies are expected. The message may become clearer if the contents of lines 133-135 could be provided after the current line 141.<br><br>Proposed change (if any): **5. Indications / treatment goals**<br>[...] | Partly accepted. This section has been revised. |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| | | In order to obtain an indication for “treatment of active ulcerative colitis”, efficacy in both “induction of remission” as well as “maintenance of remission” should be demonstrated.<br><br>~~Depending on the properties of the drug (i.e. not suitable for long term treatment or not suitable for acute treatment) separate indications for “induction of remission” or “maintenance of remission” may be granted.~~<br><br>The treatment of active disease/induction of remission, and the treatment for maintenance of remission/prevention of relapse may be studied either in separate trials or trials that combine induction treatment with maintenance treatment. While a “treat through” design may be acceptable the design of the study will have implications for the indications that can be claimed. Only separate investigation of induction of remission and maintenance of remission would allow claims for separate indications for induction and maintenance of remission.<br><br><u>Depending on the properties of the drug (i.e. not suitable for long term treatment or not suitable for acute treatment) separate indications for “induction of remission” or “maintenance of remission” may be granted.</u><br>[...] | |
| 157-159 | 2 | Comments: Please suggest such a rigorously validated instrument or in the absence of this, acceptable instruments. | Not accepted. The required information is already there, including an acceptable instrument. |
| 188-190 + 194 | 2 | Comments: It is difficult to understand how symptomatic remission and mucosal healing can be both primary endpoint and | Partly accepted. The secondary endpoint includes individual patients who achieve both mucosal healing |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| | | first secondary endpoint. | and symptomatic control. The primary endpoint is based on the population, i.e. it is required that a significant effect on a population level is achieved for both endpoints (for this analysis the patients achieving one endpoint may not necessarily be the same as the ones who achieve the other). Text has been revised to clarify |
| 197-199 | 2 | Comments: Further explanation would be helpful for the sake of comprehensibility. | Accepted |
| 205-206 | 2 | Comment:<br>Time to remission and time to response only works with symptom scores as repeat colonoscopies/sigmoidoscopies (others than at baseline and primary endpoint) are not feasible.<br><br>Proposed change:<br>• Time to remission (symptom scores or biomarkers only)<br>• Time to response (symptom scores or biomarkers only) | Accepted |
| 211 | 2 | Comment: “Steroid sparing effect” should include median dose of steroids at the endpoint. | Partly accepted. The endpoint “steroid sparing effect” has been removed as the ultimate goal of all studies. In long term studies the ultimate goal is steroid free remission. |
| 216-218 | 2 | Comment: How to define mild, moderate and severe? | Partly accepted. The definition depends on the instruments used. Text has been amended to reflect this. |
| 217 | 2 | Comment: Stratification according to mucosal inflammation (e.g. mild, moderate, severe) is recommended.<br>Patients at study inclusion have to have a score of 2/3 (for induction studies) or 0/1 (for maintenance studies). These scores | Partly accepted. Text has been amended to suggest stratification based on disease activity in general (symptoms and endoscopic score) |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| | | cannot be subdivided into mild, moderate or severe. Replacement by disease extent may be an alternative, which would require full colonoscopy at screening. | |
| 219 | 2 | Comment: How to score extra intestinal symptoms? | Accepted. Sentence has been removed. |
| 221-222 | 2 | Comment: It should be specified how mode of delivery should be taken into account | Accepted. Sentence has been removed. |
| 224-241 | 2 | Comment:<br>State that this only applicable for NCEs and new biologics. | Not accepted. Pharmacokinetic studies may be relevant for old CE with a new formulation. The extent of these studies is always determined on a case by case basis. |
| 245-248 | 2 | Comment: Addition of numbering could improve the readability of the enumeration at the beginning of the sentence (as an example see also lines 105-106).<br><br>Proposed change:<br>In the absence of 1) withdrawal of consent, 2) clinical deterioration or 3) failure to improve (according to pre-defined definitions for treatment failures), treatment under double-blind conditions should continue until the completion of the active treatment period. | Accepted |
| 259 | 2 | Comment: Symptom control is an unspecific new term. Either clinical relevant improvement (e.g. defined via MAYO) or remission. | Accepted. Text has been revised. |
| 260 | 2 | Comment: Follow-up period off-treatment to see if patients in remission at end of treatment remain in remission. In clinical practice patients do not stay off treatment after induction of remission (see ECCO Statement 6B in Medical management of active ulcerative colitis: Maintenance treatment is recommended for all patients [EL1a, RG A].. This may represent a high obstacle | Accepted. |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| | | for recruitment when patients know that they won't get anything for a certain period of time.<br><br>Proposed change: Delete sentence "An 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, unless the patients are continuing the treatment in a re-randomised or continued maintenance study." | |
| 275 | 2 | Comment:<br>a) A Mayo score of 6-12 excludes the mild patient population.<br>b) 'Text: a score of 6-12 in the clinical part of the Mayo Score'. The clinical part has a maximum score of up to 9.<br><br>Proposed change: A score of 5-12 in the Mayo Score (takes care of a) and b)) | Accepted |
| 297 | 2 | Comment: How should insufficient response be documented? | Partly accepted. The text has been revised to include guidance |
| 299 | 2 | Comment: The requirement "minimum time from diagnosis should be at least 3 months at inclusion" (line 280/281) appears contradictory to "naïve" | Not accepted. It is stated that shorter periods may be acceptable (for naïve patients) provided adequately justified. |
| 304 | 2 | Comment: Placebo control would only be accepted by ECs for trials with an add-on design | This point is not relevant as the section has been revised. |
| 308 | 2 | Comment: Information on topically acting steroids could be added. | This point is not relevant as the section has been revised. |
| 319 | 2 | Comment: "TNF-experienced patients": clarification whether this includes primary non-responders, secondary non-responders and intolerant patients may be helpful. | This point is not relevant as the section has been revised. |
| 323-324 | 2 | Comment: Patients in remission without any treatment have a | This point is not relevant as the section has been |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| | | low risk of relapse. | revised. |
| 324 | 2 | Comment: It is medical standard to provide preventative treatment in UC so not only patients in remission without any treatment are an option but also the switch from existing maintenance treatment to test and placebo (see also comment above). | This point is not relevant as the section has been revised. |
| 333 | 2 | Comment: For products where safety is already established a 6-month study may suffice | This point is not relevant as the section has been revised. |
| 335 | 2 | Comment: “Patients who are in steroid free remission are eligible for inclusion into the (maintenance) trial.”<br>Contradiction to line 395, to be clarified | This point is not relevant as the section has been revised. |
| 355 | 2 | Comment: “steroid free remission maintained without surgery throughout at least 12 months” is considered difficult to achieve, will greatly increase the numbers of patients needed at entry. | Accepted |
| 356-358 | 2 | Comment: We agree that time-to-event analysis for superiority studies in the maintenance setting is not adequate. However, it may be an appropriate statistical approach for the primary endpoint in non-inferiority studies due to assay sensitivity considerations.<br><br>Proposed change (if any): Time to event analysis is only considered supportive **in superiority studies** as just pronlonging time to relapse without decreasing the end of study risk is not considered a relevant benefit. | This point is not relevant as the section has been revised. |
| 379-381 | 2 | Comment: Complete wash-out is a problem with newer medicinal products (e.g. etrolizumab) that have a very long half-life. | Not accepted. The text states that “adequate washout period based on the pharmacodynamics effect… should be ensured”. It does not require complete washout. |
| 393-396 | 2 | Comment: This is not consistent with having steroid free remission as the primary endpoint for induction. | Accepted. |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| 395 | 2 | Comment:<br>“patients who have not been tapered before or within the induction phase should have their steroids tapered within 12 weeks after entering the maintenance phase.” This is contradictory to line 335. | Accepted |
| 396-397 | 2 | Comment: “If bridging to AZA/MP”: this is not a valid concept anymore. | Accepted. |
| 11 | 3 | Comments: Keywords: I suggest deleting "Crohn's disease" and adding "Ulcerative colitis". | Accepted. |
| 69 | 3 | Comments: It is stated that "Surgery with colectomy... is thus reserved for acute severe (fulminant) colitis or resistant cases and in some cases as cancer prevention". Colectomy is not, actually, indicated for the prevention but for the treatment of cancer. | Not accepted. If severe dysplasia is present (in flat mucosa), proctocolectomy is recommended (se ECCO guidelines) |
| 71 | 3 | Comments: long-term pouchitis risk is much higher than 30% (up to 46% in Ferrante et al, IBD 2008) | Accepted. |
| 99 | 3 | Comments: The main PROs in UC are diarrhea and rectal bleeding, but not abdominal pain nor abdominal cramps. | Not accepted. This section does not deal with PROs but symptoms in general. |
| 122 | 3 | Comments: Although it is true that according to the ECCO guideline, patients who have active disease despite prednisolone of up to 0.75 mg/kg/day over a period of 4 weeks are considered refractory to corticosteroids, this period of time is clearly too long. | Partly accepted. This section has been changed to give general recommendations. |
| 124 | 3 | Comments: It is stated that "Patients are refractory to azathioprine/6-mercaptopurine if they continue to have active disease despite at least 3 months of treatment with a sufficient dose". I suggest to include a 3-6 (instead of 3) month period, as it has already done in the CD document. | Partly accepted. This section has been changed to give general recommendations. |

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| 129 | 3 | Comments: include definition of endoscopic response and mucosal healing, not only using Mayo score but also UCEIS (since the guidelines refer to this scoring as well) | Not accepted. The guideline is not intended to give a complete description of all possibilities. Mayo is stated just an example. |
| 179 | 3 | Comments: although in the introduction the guidelines also mention UCEIS, this score is not used in the rest of the document, e.g. definition of primary endpoint | Partly accepted. Please see above |
| 205-212 | 3 | Comments: add UC related hospitalization | Partly accepted. The list of secondary endpoint is not intended to be exhaustive. Other secondary endpoints may be included provided that they are adequately justified. Text has been amended to include this option. |
| 275 | 3 | Comments: It is stated that "a score of 6-12 in the clinical part of the Mayo score may be used as an inclusion criterion". However, the clinical (non-endoscopic) Mayo score can be 9 maximum. Please check (total Mayo score?). | Accepted. |
| 282 | 3 | Comments: It is pointed out that "Shorter duration of disease has to be justified and care must be taken to avoid inclusion of patients with diarrhoea due to other causes e.g. infections and Crohn's disease". I suggest deleting "Crohn's disease", as this possibility is generally not ruled out in the short term (3 months). | Accepted. |
| 289 | 3 | Comments: It is stated that "clinical trials aiming at supporting a first line indication should always include comparison with the accepted first line treatment. Unless the study is aiming at demonstrating superiority against an existing treatment, it is critical that assay sensitivity can be demonstrated, ideally by adding a placebo arm". There seems to be a contradiction here (with the placebo inclusion/exclusion). | Not accepted. One of the ways of securing assay sensitivity is adding a placebo arm (please refer to relevant ICH guideline). |
| 304 | 3 | Comments: It is pointed out that "However, the option of a 3-arm trial with placebo and an active comparator, where the latter | Partly accepted. Placebo may be ethically justifiable provided adequate rescue procedure are in place. Text |

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| | | would serve as an internal reference (not requiring formal non-inferiority) may be acceptable in certain circumstances". However, I think the inclusion of placebo here is not acceptable. | has been amended to state that …"if ethically justifiable" |
| 336 | 3 | Comments: can patients with ongoing rectal bleeding be included in maintenance study? I suppose not, and therefor this should be clarified. | Partly accepted. Only patients who are in remission or have responded can be included in the maintenance trial. Response should be defined and justified according to the instruments used. The text has been modified to state this |
| 369 | 3 | Comments: It is stated that "For a first line indication of maintenance of remission, the efficacy of maintenance therapy in this patient population should be determined by placebo-controlled trials if ethically justifiable". However, as 5-ASA have been demonstrated to be clearly effective, these drugs should be included as comparator instead of placebo. | This point is not relevant as the section has been revised. |
| 372 | 3 | Comments: can vedolizumab not be a comparator in UC? | Partly accepted. The text has been modified to give more general recommendations without specifically rule one specific comparator in or out. |
| 419 | 3 | Comments: it would be interesting to see the effect of concomitant immumodulatory therapy on the development of anti-drug antibodies | Accepted. |
| 563 | 3 | Comments: what is mucosal healing in case of pouchitis? | Not accepted. The guideline specifically states that there is lack of knowledge in this field. |
| 98-110 | 4 | 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 | Partly accepted. It is already stated that patients should be included into trials based on a recent endoscopy (within one month) |
| 102-103 | 4 | 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 | Not accepted. Histology should be included for confirmation of UC activity and exclusion of other causes, e.g. CMV. |

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| | | 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 | 4 | 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.<br><br>Proposed Change: Please change “3 months” to “6 weeks.” | Partly accepted. The text has been modified to give general recommendations and make reference to specific definitions in Guidelines from learned societies. |
| 125 | 4 | 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.<br>Suggest making definition(s) of remission consistent with those used in clinical practice and also FDA draft guidance.<br><br>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. | Partly accepted. The text has been modified to state what is meant by remission (symptomatic and endoscopic). |
| 131-132 | 4 | **Comment:** Why is the indication “treatment of active ulcerative colitis” and not “treatment of ulcerative colitis”, as it includes maintenance of remission?<br><br>Why only “maintenance of remission” and not “remission or sustained remission”? | Partly accepted. The text has been modified but with similar but not exact wording in line with previous indications granted by the CHMP. |

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| | | Proposed change (if any):<br>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 | 4 | 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"<br><br>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 | Accepted. |

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| | | treatment for a longer time, with ongoing observation to ensure there is sustained benefit.<br><br>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).<br><br>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.<br><br>Additional comments regarding the appropriateness of treat-through vs. randomized withdrawal maintenance studies are provided in response to Lines 340-353.<br>**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 | |

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| | | an indication for “treatment of active ulcerative colitis”. | |
| 136-141 | 4 | Comments: 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. | Accepted. |
| 138 | 4 | Comment: While a “treat -through” design may be acceptable the design of the study will have implications for the indications that can be claimed.<br>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<br><br>Proposed change (if any): Please clarify the type of indication granted in case of treat-through design.<br>Also further define “treat-through” | Accepted. |
| 147-148 | 4 | Comments: 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) | Not accepted. There is a tight coupling between inflammation and mucosal healing. A drug that affects healing directly will have to indirectly reduce inflammation otherwise the effect will not be durable. The guideline as written is still relevant in this |

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| | | | situation. |
| 152-159 | 4 | 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.<br>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).<br><br>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? | The distinction between signs and symptoms is to some extent arbitrary. E.g. having diarrhoea, which is both a symptom (patient feeling it) and a sign (the doctor/nurse can see it but so can the patient). The text clearly states that option B is the recommended. |
| 152-159 | 4 | 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 | Not accepted. This falls outside the scope of the current guideline. |

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| | | 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” | |
| 152, 166-167 | 4 | Comment: Please use “patient reported outcomes” and not “patient related outcomes”<br><br>Proposed change (if any):<br>“Symptomatic relief should be evaluated by patient ~~related~~ reported outcomes (PRO).”<br>“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.” | Accepted. |
| 152-159 | 4 | 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 | Partly accepted. The text has been modified but with similar but not exact wording in line with previous indications granted by the CHMP. |

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| | | 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.<br><br>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 | 4 | Comments: 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 | No accepted. It is stated clearly in the guideline |

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| | | 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 | 4 | 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.<br><br>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. | Not accepted. The intention of the guideline to request significant effects on both aspects would be invalidated if the proposed changes were implemented. The sponsor is free to collect and report the total index as a secondary endpoint |
| 169-170 | 4 | 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?<br><br>Proposed change (if any): See above. | The guideline is open for inclusion of adequately justified secondary endpoints. Generally, effects on secondary endpoints will not be reflected in the label but can be mentioned in section 5.2 of the SPC |
| 172-192 | 4 | 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 | Not accepted. The guideline is clear that remission should be the primary endpoint. However, the guideline also states that responders may be included into the maintenance part of the studies. |

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| | | 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.<br><br>Proposed change (if any): Agency to clarify if clinical response can be accepted as primary endpoint | |
| 173 | 4 | 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.<br><br>Proposed change (if any): Consider changing steroid free | Partly accepted. Tapering of steroids during induction is indeed feasible as documented by a recently published study. From a patient safety perspective, this is a recommendable approach. Nevertheless, the guideline has been modified to allow fixed steroid dose during the induction phase, provided that this does not pose an undue risk to the patient (dosage and duration should be justified). |

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| | | remission to “an appropriate goal of treatment and an appropriate secondary endpoint”. | |
| 173-176 | 4 | Comment: Text in lines 173-176 does not include text regarding induction/maintenance of a clinical response<br>‘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.’<br><br>Proposed change (if any):<br>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. | Not accepted. Please see previous response regarding response as a primary endpoint. |
| 174-176 | 4 | 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 | Not accepted. The guideline should not mandate fixed high doses of corticosteroids (due to potential side effects). As currently worded, inclusion of patients on high doses is indeed possible but these should be tapered. |

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| | | 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).<br><br>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 | 4 | 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. | Partly accepted. Duration has been specified. It is up to the sponsor to justify how high a dose can be administered as a fixed dose without putting subjects at risk of side effects. |
| 177-178 | 4 | 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)<br><br>Proposed change (if any):<br>Signs and symptoms are defined by stool frequency (SF = 0-1) and rectal bleeding (RB =0) | Not accepted. It is clearly stated that the definition depends on the instruments used. |
| 184-187 | 4 | 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 | Not accepted. It is clearly stated that cessation of bleeding should always be included in the definition of remission. Thus, the proposal is redundant. |

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| | | "Irrespective of scale used, the definition of remission should encompass cessation of rectal bleeding".<br><br>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.<br><br>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 | 4 | Comment: The Mayo Clinic Score is composite within a patient.<br><br>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.<br><br>Please also clarify whether re-randomization into maintenance is based on a patient achieving either or both symptomatic remission and/or MH.<br><br>Please also clarify if co-primary endpoints may be assessed at different time points.<br><br>Proposed change (if any): "As outlined above, symptomatic remission and MH should be considered composite ~~co-primary~~ endpoints." | Partly accepted. It is clearly stated that the two parts of the Mayo score is used separately and as co-primary endpoints. No changes proposed.<br>As regards the last two points: this has been clarified in section 7 |
| 188 | 4 | The Agency's Draft UC Guidance suggests a "Co-Primary" | Not accepted. The general approach of co-primary |

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| | | 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.<br><br>“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.”<br><br>“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. “<br><br>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.<br><br>“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 | endpoints is maintained. The “composite endpoint approach” is also included, however, as an important secondary endpoint. |

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| | | 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.)<br><br>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 | 4 | 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.<br><br>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. | Not accepted. The guideline is clear that remission should be the primary endpoint. However, the guideline also states that responders may be included into the maintenance part of the studies. Furthermore, response is an important secondary endpoint |
| 195 | 4 | 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.<br><br>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. | Partly accepted. Examples of definitions of remission has already been given. Definitions of response depends on the instruments used. |
| 197-200 | 4 | Comment: The revised guideline clearly indicates that "remission" | Partly accepted. The text has been modified to allow |

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| | | 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”=<br><br>Proposed change (if any): Please indicate whether the endpoints can be analysed as change from baseline | inclusion of additional secondary endpoints provided that these are adequately justified. |
| 201 | 4 | Please clarify what scales are appropriate for histological evaluation and at what time point these evaluations are expected | Currently there are no fully validated scales for this purpose. |
| 201-201 | 4 | Comment: We consider that histological improvement would be an additional valuable secondary endpoint. | Partly accepted. The text has been modified to allow inclusion of additional secondary endpoints provided that these are adequately justified. |
| 201-204 | 4 | 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).<br><br>Proposed change (if any): Evaluation of histological improvement | Not accepted. The guideline does discriminate between secondary and exploratory endpoints |

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| | | should be included as an exploratory endpoint to assess UC activity and treatment efficacy. | |
| 203 | 4 | 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.<br><br>Proposed change (if any): Consider removing. | Accepted |
| 203-204 | 4 | 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.<br><br>Please clarify what is meant by normalisation of CRP, as many patients do not have elevated CRP levels.<br><br>Please clarify what label claim this endpoint supports.<br><br>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". | Accepted. |
| 208 | 4 | 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 | Not accepted. Outside the scope of the current guideline. Reference is made to the relevant general guidance document. |

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| | | 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?<br><br>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 | 4 | 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”.<br><br>Proposed change (if any): Consider removing. | Partly accepted. It has been stated that this primarily relevant in acute, severe UC. |
| 213-215 | 4 | 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.<br>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.<br><br>Proposed change (if any): Consider changing corticosteroid free | Not accepted. The aim of treatment should be cortico-free remission. Keeping patients on steroids and not even achieving remission is not a useful endpoint. Patients who can only achieve a response when on long-term steroid treatment should be considered for colectomy. |

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| | | 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 | 4 | 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.<br><br>Proposed change (if any): Consider making a statement on the minimum duration of steroid-free remission (or response) required to meet these endpoints. | Not relevant as text has been modified. |
| 218 | 4 | 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).<br>We consider the Mayo score is more appropriate than the anatomical location (i.e. mild=1, moderate=2, severe=3).<br><br>Proposed change (if any):<br>“…e.g. ~~**mild, moderate and severe**~~ **by MCS, ES, or UCEIS.**” | Accepted. |
| 273 | 4 | Comment: Stipulates that subjects entering trials must have had “recent visualization of their GI tract” but does not stipulate what is meant by “recent”.<br><br>Proposed change: Propose recommendation for what is considered "recent". | Accepted. |
| 275-276 | 4 | Comment: 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 | Accepted. This has been done in section 7.2.2.2.2. |

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| | | acceptable to define disease for inclusion. Also, is the range specified in this sentence intended to define only moderate to severe disease? | |
| 284 | 4 | Comment: We do not agree with the recommendation that the primary endpoint of an induction study should be steroid free remission.<br><br>The reasons to maintain stable corticosteroid doses during the induction period include the following:<br>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.<br>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.<br><br>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.<br><br>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. | Partly accepted. Tapering of steroids during induction is indeed feasible as documented by a recently published study. From a patient safety perspective, this is a recommendable approach. Nevertheless, the guideline has been modified to allow fixed steroid dose during the induction phase, provided that this does not pose an undue risk to the patient (dosage and duration should be justified). |

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| | | In some UC clinical trials, corticosteroid tapering is mandatory in clinical responders using defined criteria over a longer time period during the maintenance period.<br><br>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.<br><br>Proposed change: Delete reference to steroid taper during induction. | |
| **Additional related comments:**<br><br>262-263<br><br><br><br>284 | 4 | Comment: 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.<br><br>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. | Partly accepted. Please refer to previous responses on the same topic. |
| 286-292 | 4 | Comments: In active comparator studies with a placebo, please | The problems described are acknowledged. The section |

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| | | clarify which comparison is expected to support approval—versus placebo? Or the active comparator? | has been rewritten |
| 318-319 | 4 | Comments: 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.<br>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 | The problems described are acknowledged. The section has been rewritten. |
| 324-326 | 4 | 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? | Not accepted. It is considered ethically justifiable to randomise patients in remission to placebo, provided that adequate escape procedures are in place. |
| 335 | 4 | 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 | Accepted. |

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| | | 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.<br><br>Proposed change: Acknowledge that patients in clinical response are an appropriate primary target population for the assessment of maintenance therapy. | |
| 335-339 | 4 | Comment: 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. | Accepted. |
| 335, 340 | 4 | 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 | Accepted. |

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| | | have protocolized weaning when they enter maintenance.<br><br>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.<br><br>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.<br><br>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.<br><br>Proposed change (if any): Consider changing these lines to reflect that patients in clinical response should be allowed to enter maintenance studies. | |
| 340-353 | 4 | Comment: Also refer to comments in response to Lines 136-141.<br><br>The notion that true maintenance of efficacy can only be | Partly accepted. The text has been modified to allow inclusion of responders into maintenance trails. Furthermore, a treat through design has been included |

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| | | 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.<br><br>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.<br><br>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.<br><br>It should be noted that comparison to standard of care comparators (e.g. anti-TNF) using this methodology incurs | as an acceptable design. Section on comparators has been revised. However, randomised withdrawal studies are still considered both ethically justifiable and appropriate to demonstrate long term efficacy. |

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| | | 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.<br><br>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 | 4 | 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 | Partly accepted. Please refer to previous responses |

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| | | important measures of the effectiveness of a maintenance therapy.<br><br>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.<br><br>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 | 4 | Comments: 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 | Accepted. |
| 370-372 | 4 | Comments: 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 | Accepted. |

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| | | 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 | 4 | Comments: 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. | Accepted. |
| 382-392 | 4 | Comments: 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? | Accepted |
| 395-396 | 4 | Comment: Please clarify if the one year maintenance phase can include 12 weeks of steroid tapering at the beginning of the maintenance phase.<br>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. | Accepted. |
| 431 – 433 | 4 | 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) | Because of limited number of patients in the lower age category, if UC is presenting, minimal number of probands is acceptable. Attempt of stratification on age and BW should be done. |

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| 431-437 | 4 | 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.<br><br>Proposed change (if any):<br>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.<br>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. | There is no reason to explicitly exclude patients with VEOIBD.<br>Age at the dg accepted |
| 436-437 | 4 | Comment: Please clarify the term "younger children" by adding | Accepted |

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| | | an age.<br>We agree to genetically testing children, but should not be the sponsor´s burden.<br><br>Proposed change (if any):<br>"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 | 4 | Comments: 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.<br><br>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 | Not accepted, extrapolation GL are not defined, details are not supported by any data. |
| 488-489, 492-493 | 4 | Comments: 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 | Not accepted, endoscopies in clinical practice are not so frequent, but for study purpose especially with new products are essential |

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| | | 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 | 4 | 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.<br><br>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?<br><br>Would it be acceptable to separate endoscopy from the induction/maintenance paradigm (i.e. perform endoscopy at the 6 month time point)?<br><br>Or Please clarify, if endoscopy has been shown in adults, can it be waived in children?<br><br>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)? | See also comments above. Endoscopies should not be waived, but in combined studies, second endoscopy could be performed during maintenance phase. |
| 504-519 | 4 | When extrapolation is not possible, a non-inferiority trial cannot be operationalized in terms of the choice of the non-inferiority margin.<br><br>Proposed change (if any): explain whether the margin can be based on the adult trials (from which extrapolation cannot be | When general guidance is not applicable, scientific advise (CHMP, PDCO) on the particular case is encouraged. |

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| | | used) or other paediatric trial in the same indication. | |
| 505 | 4 | 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.<br><br>Proposed change (if any): The paragraph on placebos in pediatric studies may have to be re-written to reflect current expert guidance. | Not accepted, article is not expert GL, more than opinion and not supported by the dates. |
| 515-516 | 4 | Comment: Please clarify, what is the risk of "lack of efficacy"?<br><br>Proposed change (if any):<br>"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". | Accepted |
| 520-521 | 4 | 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. | There is no need to provide any further GL, up to the applicant |
| 536-538 | 4 | 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. | Not accepted, impact on vaccination is general terminus technicus |

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| | | 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 | 4 | Comment: Please clarify " if a cross company registry" or a "cross paediatric GI registry established by a professional organisation such as ECCO" is intended | GI professional org registry would be better, but not necessary |
| Sections 8.3.1.1 – 8.3.1.5 | 4 | 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. | Age range from 2 years above should be covered |
| 11 | 4 | Comment: Suggest to add 'ulcerative colitis' | Accepted |
| 32 | 4 | 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" | Accepted |
| 107 | 4 | 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.<br><br>Proposed change (if any): Delete "includes" | Accepted |
| 182-183 | 4 | Comment: Please describe how "standardization of reading should be convincingly demonstrated" can be demonstrated (what is expected?) | It is outside the scope of guideline to provide detailed advice on this subject. |
| 201-202 vs 204 | 4 | Comment: Please define "histological normalisation".<br>What is the difference between "histological normalisation" and "histological remission"? | Accepted |

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| | | We suggest to use the same terminology. | |
| 211 | 4 | Comment: Please clarify how steroid sparing effect is different from the primary endpoint. | There is no difference, the secondary endpoint has been removed. |
| 260-262 | 4 | 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. | Accepted |
| 262-264 | 4 | 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.”<br><br>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. | Accepted |
| 280-281 | 4 | Comment: 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. | Accepted |

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| 325 | 4 | Comment: “Patients who are presently on the test drug should be randomised to continuing the test drug or switching to …”<br>It seems clear from the chapter 7.2.2.2.2 below that re-randomisation is what is meant in this sentence<br><br>Proposed change (if any): Patients who are presently on the test drug should be re-randomised to continuing the test drug or switching to … | Accepted |
| 340-346 | 4 | Comment: text on lines 340 -346<br>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. However, if the intended claim is “maintenance of remission”, the primary analysis should be based on the remitters only.<br><br>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. | Not accepted. Maintenance of response is not a relevant indication. |
| 393-394 | 4 | Comment: The tapering schedule given should specify the | Accepted |

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| | | pertinent group of steroids. As commented earlier, there are different groups/compounds which may require different schedules. | |
| 400-401 | 4 | 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.<br><br>Proposed change (if any): The sentence on lines 400-401 should be amended or removed. Clarification is required. | Accepted |
| 402 | 4 | Comment**: Treatment with antibiotics should be at the discretion** of the sponsor.<br><br>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". | Not accepted. Not understood. Why at the discretion of the sponsor? At the discretion of the treating physician? |
| 402-404 | 4 | Comment: 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 | Accepted |
| 422 | 4 | Comment: "Furthermore, it is important to get information on re-treatment outcomes even after a longer time interval without treatment with a specific drug."<br>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 | Accepted |

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| | | 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 | 4 | Comment: Please clarify that paediatric Ulcerative Colitis is a rare disease in younger children.<br><br>Proposed change (if any):<br>"**Paediatric** UC is **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." | Not accepted |
| 488 | 4 | Comment: Please clarify that clinical remission is the same for both adults and children. | Clinical remission in paediatric patients is well defined |
| 488-489 | 4 | Comment: Please clarify that clinical remission and endoscopic MH could be separated in time.<br>How do you re-randomize, based on the co-primary endpoint?<br>Can you re-randomize based on response? | Only response is not acceptable |
| 492-493 | 4 | Comment: Please clarify that endoscopy can be performed within a subset of patients. | According to the current knowledge, recommendation to study MH only in subgroups cannot be made |
| 495-496 | 4 | 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", | Not clear, until reliable pediatric index is developed PUCAI is prefered |

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| | | does the agency have any advice on when to utilise the PRO and the ClinRO version of the PUCAI?<br><br>Proposed change (if any): clarify which version of the PUCAI EMA recommends for paediatric studies | |
| 498-499, 500-503 | 4 | Comments: “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. | Not accepted. In growing organisms, pediatric population, is free steroid remission adequate. |
| 510-514 | 4 | Comments: 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). | Not accepted |
| 530-532 | 4 | Comment: Please specify “development”. We propose to change the wording to “growth velocity”<br><br>Proposed change (if any):<br>“Post-study/post authorisation long-term data, either while | Not accepted, growth velocity is a part of development, general wording… |

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| | | 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 | 4 | Comments: Does this need for long-term safety data in growing children mandate the need for post-approval registries? | No |
| 543 | 4 | Comments: 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? | Not necessary |
| 126-129<br>164-168 | 5 | Comment: The agency's use of endoscopy as evidence of mucosal healing is not aligned with FDA guidance that states that mucosal healing can only be assessed via histology and that endoscopy assessments will only provide the ability to claim "improvement on endoscopic appearance". This will also require the guidance to be updated to reflect how induction of remission should be assessed before re-randomization.<br><br>Proposed change (if any): Align definitions of mucosal healing with global expectations such that data can be analysed and used consistently across markets from the same trial data set. | Not accepted. The definition of mucosal healing (in the present document) being based on endoscopic appearance is in line with the scientific literature (e.g. D'Haens G, Sandborn WJ, Feagan BG, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology. 2007;132:763–786. |
| 131-135 | 5 | Comment: The distinction between induction and maintenance has been historically carried over from drugs with long times to onset or drugs designed specifically for short term use. The distinction is not applicable to new classes of agents intended for both short term and long term use (i.e., small molecules with quick onset of action). Induction and maintenance studies require withdrawal of therapy from subjects who are responding. A treat-through design permits treatment without withdrawal of | Accepted |

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| | | therapy for subjects responding to drug and is more appropriately suited to the vast majority of moderns drugs in development (e.g. small molecules).<br><br>Proposed change (if any): In order to obtain an indication for treatment of active ulcerative colitis, adequate exposure and length of treatment would be required with endpoints assessed at both early and late time-points. Treat through design can address need for claims. | |
| 188-189<br>200-202<br>277-279<br>343-345 | 5 | Comment: While it is acknowledged that the use of only 'treat-though' designs would impact the labelling and indications that could be claimed at the time of Marketing Authorisation Application, an argument could be made for the use of one induction and maintenance study (in e.g. TNFa inhibitor-experienced subjects) and a separate 'treat-through study' (in e.g. subjects naïve to TNFa inhibitor). Together, these studies provide complementary data at early and late time points, proof of maintenance of effect, and limit the withdrawal of drug from responding subjects.<br><br>Proposed change (if any): Provide clear, expected study designs for registration. | Accepted |
| 142 | 5 | Comment: Steroid sparing is considered a key endpoint as described within the guidance and should be able to be part of an indication statement.<br><br>Proposed change (if any): Steroid sparing may form part of indication if data supports a steroid sparing effect. | Not accepted. The goal of treatment is remission free of steroids. To include a sentence about steroid sparing is redundant. |
| 142-144 | 5 | Comment: Much emphasis has been placed on application of | Partly accepted. The text has been modified to allow |

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| 173-192 | | steroid free clinical and endoscopic remission as co-primary end points for therapeutic studies and the need to have predefined tapering rules for patients who are on steroids at entry. However the document seems to have conflicting messages throughout. For an induction study, achieving steroid free remission is an appropriate primary end point. It is advised that induction of remission should occur by 8 weeks but symptomatic control should occur within 4 weeks, during which time patients should achieve steroid taper and be in remission in order to be included in any re-randomization to explore maintenance with a primary end point of maintenance of steroid free remission for at least 12 months. However, for short induction periods patients may remain on low dose steroids and be in remission. However, this would preclude them from being included in any analysis of the recommended maintenance primary end point. This sets an extremely high bar for efficacy and provides significant challenges at induction for confounding effects of steroids v IMP.<br><br>Proposed change (if any): Provide more clarity on how steroid sparing can be calculated and used in any supporting claim and what impact short duration induction periods and their corresponding remission end points in the presence of low dose steroids will have on the ability to claim maintenance of remission | low doses of steroids in induction studies of short duration. As stated above, the long term goal is always steroid free remission. Thus any claims of avoiding steroids is redundant. |
| 173, 188, 189, 194 | 5 | Comment: Achieving/maintaining remission free of steroids may be a key endpoint but should not be defined as a primary endpoint. Clinical and endoscopic healing should remain primary endpoints. This approach was considered appropriate during recent scientific advice discussions with national agencies.<br>In line 189 an alternative co-primary endpoint is proposed; | Partly accepted. Endoscopic and symptomatic remission are co-primary endpoints (meaning that the study on a population level but not necessarily on an individual level should demonstrate a significant effect on both). Whether concomitant steroids should be allowed, depends on the type and duration of study. |

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| | | therefore, the guidance sends conflicting messages on which endpoint should be primary.<br>Finally, line 188 notes, “symptomatic remission and MH should be co-primary” and then line 194 delineates MH and symptomatic remission as a secondary endpoint. | For induction studies, steroids may be acceptable but for maintenance studies, they are not. Patients achieving both mucosal healing and symptomatic remission (at an individual level) is a secondary endpoint. The text has been amended to clarify this. |
| 308 | 5 | Comment: Placebo is an adequate comparator when considering first line indication for induction of remission. A non-inferiority study against systemic corticosteroids is not aligned with recent approvals for ulcerative colitis, including vedolizumab. | Not agreed. Please refer to previous responses |
| 1-585 | 6 | Comment: Recommendations in proposed guideline should be specified more clearly to avoid misinterpretation as much as possible.<br><br>Proposed change (if any): See above. | Accepted |
| 59 | 6 | Comment: It is advised to insert the following sentence from current EMA scientific guideline after the sentence about paediatric ulcerative colitis:<br>‘Mortality is not increased in UC in general but the disease may present as life-threatening acute severe colitis.’<br><br>Motivation:<br>It was proposed to remove a sentence about mortality from the EMA scientific guideline. This sentence is still appropriate according to medical literature (e.g. Tess et al. 2007, Andrew & Messaris 2016) and indicates the need for appropriate treatment options for ulcerative colitis. For this reason, it is advised to insert respective sentence about epidemiology in line 59 of proposed guideline. | Accepted |

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| | | Proposed change (if any): See above. | |
| 60 | 6 | Comment: It is advised to start a new paragraph with 'The mainstay of therapy for mild to moderate UC …' in order to separate epidemiology and disease characteristics from its treatment, as in current EMA scientific guideline on ulcerative colitis.<br><br>Proposed change (if any): See above. | Accepted |
| 76 | 6 | Comment: It is recommended to state within the Scope section that any deviation from the guideline should be justified, as indicated in current EMA guideline on ulcerative colitis.<br><br>Proposed change (if any): See above. | Not accepted. This is true for all guidelines, not specific for this one. |
| 138-139 | 6 | Comment: Effects of study treatment with respect to induction of remission and maintenance of remission should be evaluated in separate studies (see General comments above). Hence, 'threat through' design is not recommended.<br><br>Proposed change (if any):<br>The sentence '*While a 'treat through' design may be acceptable the design of the study will have implications for the indications that can be claimed.*' should be removed. If this is not agreed, potential implications of a 'treat through' design for proposed indications should be specified in the guideline. | Not accepted. The treat through design reflects current treatment practice and is in line with guidance given for other chronic inflammatory disorders. It is agreed that a treat through design will have implication for the indication which can be claimed. |
| 172-192 | 6 | Comment: Definitions of (co-)primary and major secondary endpoints need to be specified more clearly for appropriate implementation in clinical studies (see general comments above).<br><br>Proposed change (if any): *6.1.1.1.* Co-p~~P~~rimary endpoints | Partly accepted. The text has been revised largely, but not completely as suggested. The term "if possible without concomitant steroid treatment" has been removed as it can be interpreted as option for evaluating long term effects on concomitant steroids. |

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| | | Treatment of ulcerative colitis is aimed at inducing and maintaining both symptomatic and endoscopic remission, if possible without concomitant steroid treatment.<br><br>Because of this, co-primary endpoints of both induction and maintenance treatment should concern:<br>(1) the proportion of patients with symptomatic, and<br>(2) the proportion of patients with endoscopic remission.<br><br>Important secondary endpoints concern the proportions of patients in whom either or both of these co-primary endpoints are met without or at particular doses of steroid treatment (see below). Further, the change in use of corticosteroids – especially in the maintenance phase – is of interest.<br><br>~~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.~~<br><br>*Remission should be defined and justified according to the instruments used for evaluating signs and symptoms and inflammation, respectively. E.g. when mucosal inflammation is evaluated by the Mayo sub score, a score of 0 or 1 may be used for defining endoscopic healing. Whereas the more stringent definition is preferred, the less stringent definition could be* | Furthermore, the text has been amended to clarify when remission on steroids is acceptable and when it is not. |

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| | | *acceptable, based on the pharmacodynamic (PD)-properties of the investigational compound and/or the patient characteristics (e.g. severity). Adjudication of endoscopic evidence of activity should be performed, preferably by central reading of the examinations. If decentralised reading of examination is performed, standardization of reading should be convincingly demonstrated.*<br><br>*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. Irrespective of scale used, the definition of remission should encompass cessation of rectal bleeding.*<br><br>*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. *The timing of measuring the primary endpoint depends on the aim of the treatment (please see below) as well as the pharmacodynamic properties of the test drug.*<br><br>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. | |
| 193 | 6 | Comment: Ultimate treatment goal of ulcerative colitis treatment concerns induction and subsequently maintenance of remission | Partly accepted. The rule should be that the primary endpoint is remission free of steroids. Remission with |

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| | | without the use of steroids. Hence, proportions of patients in whom either or both co-primary endpoints symptomatic and endoscopic remission are achieved without concomitant steroid treatment concern important secondary endpoints. Even if remission can only be achieved with concomitant steroid treatment, the dosage of steroid treatment at which remission is obtained is informative about the efficacy of study treatment. Because of this, it is recommended that doses of steroid treatment at which remission is obtained are reported. Respective secondary endpoints should be evaluated in all clinical studies in which concomitant steroid treatment is allowed.<br><br>Proposed change (if any):<br>The following text should be inserted at the start of the secondary endpoint section:<br>Treatment of ulcerative colitis is aimed at inducing and maintaining both symptomatic and endoscopic remission, if possible without concomitant steroid treatment. Since co-primary endpoints have been defined with respect to symptomatic and endoscopic remission itself (see above), important secondary endpoints concern:<br>- proportions of patients in whom either or both symptomatic and endoscopic remission are achieved without concomitant steroid treatment.<br>- proportions of patients in whom either or both symptomatic and endoscopic remission are achieved at particular doses of concomitant steroid treatment (e.g. 5, 10, 20, or higher doses). | (or without) steroids is acceptable only in short term induction studies when tapering of steroids is impracticable. The proposed text weakens this message and is consequently not included. However, it is stated that if the study allows steroids, proportion of patients achieving remission without steroids is a relevant secondary endpoint. |

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| | | These endpoints should be evaluated in all clinical studies in which concomitant steroid treatment is allowed.<br><br>Other recommended secondary endpoints concern:<br>• *Patients achieving both MH and symptomatic remission*<br>(…)<br><br>~~In patients who are steroid dependent, withdrawal of the steroids may be the objective. The primary endpoint should be the number of patients in clinical and endoscopic remission in whom steroids could be withdrawn.~~ *Procedures for withdrawal (e.g.~~,~~ tapering schedules) should be predefined.*<br><br>(…) | |
| 194 | 6 | Comment: Some secondary endpoints in current EMA guideline on ulcerative colitis such as 'changes in stool frequency', 'disappearance of visible blood in faeces', and 'urgency' are still considered relevant for evaluating treatment efficacy, as bloody stools, increased frequency of bowel movements, incontinence, and diarrhoea are common signs and symptoms of ulcerative colitis (Ungaro et al. 2016). These secondary endpoints should therefore be included in revised EMA guideline on ulcerative colitis.<br><br>Proposed change (if any): See above. | Partly accepted. There are validated scales for evaluation of urgency. This is not included. Disappearance of blood in stool is included in the co-primary endpoint. This is not included. |
| 211 | 6 | Comment: It is recommended to evaluate the proportions of patients with particular dose decrements of concomitant steroid treatment (e.g. 0, 5, 10, 20 mg, or even higher). Based on the comments with respect to line 193, it is recommended to adjust | Partly accepted. For studies where steroids are not tapered at time of evaluation, this is already included. For other studies, it is not relevant. |

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| | | proposed secondary endpoint on steroid sparing effects.<br><br>Proposed change (if any): *Steroid sparing effect such as:* ~~Proportion in steroid-free remission;~~specification of proportions of patients with particular dose decrements of steroid treatment (e.g. 0, 5, 10, 20 mg, or even higher) compared to baseline. | |
| 264 | 6 | Comment: The extra dot prior to 'As previously stated' should be removed.<br><br>Proposed change (if any): *… goal of therapy. ~~.~~As previously stated …* | Accepted |
| 302 | 6 | Comment: The extra dot after 'remission.' should be removed.<br><br>Proposed change (if any): *maintenance of remission.~~.~~* | Accepted |
| 340-349 | 6 | Comment: See general comment above with respect to induction and maintenance treatment.<br><br>Proposed change (if any): It is proposed to remove lines 340-349 (*Trials of combining … 'maintenance of efficacy'.*). | Not accepted. See previous response |
| 356 | 6 | Comment: See below.<br><br>Proposed change (if any): 'consideres' Should be replaced with 'considered.' | Accepted |
| 424 | 6 | Comment: It is proposed to add a section about geriatric patients. This is important, since geriatric compared to younger patients are more likely to experience among other factors reduced glomerular filtration rates, increased susceptibility to adverse events (e.g. delirium, fractures), and drug-drug interactions in case of polypharmacy (John et al. 2016). | Not accepted. This is general and not specific for this guideline |

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| | | In addition, a cross-reference may be added to the ICH E7 guideline with respect to the inclusion of geriatric patients in studies for medicine development.<br><br>Proposed change (if any):<br>Elderly patients<br>It should be ensured that adequate number of elderly patients are included in clinical trials, since clinical effects in these patients may be influenced by factors such as reduced glomerular filtration rates, increased susceptibility to adverse events (e.g. delirium, fractures), and drug-drug interactions in case of polypharmacy. Referred is to the ICH E7 guideline for additional guidance. | |
| 425-463 | 6 | Comment: Proposed information on the need for paediatric study data in section 8.3.1. and 8.3.1.1. may be perceived as contradictory by readers.<br><br>Motivation:<br>In lines 432-436 the importance of including paediatric patients from 2 years and above with ulcerative colitis in clinical studies is discussed. By contrast, in lines 443-444 it is stated that based on similarity of ulcerative colitis in adults and children, extrapolation of effects of study treatment of adult to paediatric patients should be considered in order to spare paediatric patients from unnecessary studies. Probably, it was aimed to make clear that the need for paediatric studies in ulcerative colitis should be carefully assessed.<br><br>Proposed change (if any): For clarity and to avoid | Not accepted<br>There is no contradiction, age range 2 -18 ys, with reduction of unnecessary studies… |

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| | | misunderstanding, the discussion on the need for paediatric studies should be integrated. | |
| 486-503 | 6 | Comment: Like in adult patients, co-primary endpoints of pharmacological treatment of paediatric patients with ulcerative colitis should concern the proportion of patients in symptomatic remission, and endoscopic remission (i.e. mucosal healing) respectively. The term 'symptomatic remission' is more appropriate to define symptomatic remission than 'clinical remission.' As it can not be excluded that growth and maturation are reduced in paediatric ulcerative colitis patients (Malmborg & Hildebrand 2016), absence of side effects on growth and maturation should be evaluated with respect to each of these co-primary endpoints. As in adults, secondary endpoints should include the proportion of patients meeting the primary endpoint either without or at particular dose(s) (reductions) of steroids.<br><br>Proposed change (if any):<br>***8.3.1.3. Efficacy in paediatric patients***<br><br>*Studies in children should aim for achieving remission without side effects on growth and maturation. Remission should be defined as clinical remission accompanied by endoscopic MH.* Symptomatic~~Clinical~~ *remission and endoscopic MH* with no evidence of side effects on growth and maturation *should be used as co-primary endpoints.*<br><br>~~Clinical~~Symptomatic *response alone in children is not considered acceptable as primary endpoint in respect of the longevity of the disease in this age group and colectomy with an ileo-anal pouch* | Not Accepted. Strict steroid free remission is crucial in growing organisms.<br>Clinical remission means symptoms and signs, which are the real meanings in GL |

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| | | *as alternative.*<br><br>*For induction/ maintenance trials representative changes in mucosal appearance are expected to be evaluated, therefore endoscopy is required.*<br><br>*Endoscopic MH should be assessed by the Mayo score (score of 0, or ≤1).*<br><br>*Because a validated paediatric PRO (pPRO) for the evaluation of symptoms is not currently available, for the time being, the use of the PUCAI as a surrogate for symptomatic remission is considered acceptable.* ~~Clinical~~Symptomatic *remission can therefore be defined as* the proportion of patients with *PUCAI<10 points* with no evidence of side effects on growth and maturation.<br><br>~~The primary endpoint of maintenance trials should be sustained relapse-free corticosteroid-free remission (defined as maintaining both, symptomatic clinical remission, and endoscopic MH).~~<br>As in adult patients, important secondary endpoints in paediatric patients concern the proportions of paediatric patients in whom either or both co-primary endpoints are achieved without steroids or at particular dose(s) (reductions) of steroid treatment.<br><br>*In trials when endoscopy is waived, the primary outcome measures should reflect the percentage of patients achieving or maintaining corticosteroid-free* symptomatic *remission* (e.g. a PUCAI score of <10 points) with no evidence of side effects on growth and maturation. ~~Due to the sufficient amount of validation~~ | |

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| | | ~~data available with good results, the PUCAI score can be used in such a situation, with remission defined as a PUCAI score of <10 points.~~ | |
| 490-491 | 6 | The intent of the following sentence should be reconsidered and subsequently be adjusted, as it is unclear what is meant:<br><br>'*Clinical response alone in children is not considered acceptable as primary endpoint in respect of the longevity of the disease in this age group and colectomy with an ileo-anal pouch as alternative.*' | In the case of partial response, the treatment cannot be considered sufficiently effective… |
| 11 | 7 | Comment: Keywords<br><br>Proposed change (if any): delete Crohn's disease, add Ulcerative colitis | Accepted |
| 69 | 7 | Comment: Colectomy is not only indicated for the prevention, but also for the treatment of cancer<br><br>Proposed change (if any):<br>"in some cases as cancer prevention or treatment" | Accepted |
| 71 | 7 | Comment: pouchitis may occur in up to 45% (Ferrante et al IBD 2008)<br><br>Proposed change (if any): occurring in up to 45% of patients | Accepted |
| 99 | 7 | Comment: The main PROs in UC are diarrhea and rectal bleeding. Abdominal pain is not the main symptom in UC<br><br>Proposed change (if any): remove "Patients complain of pain (abdominal cramps), urgency and bloody diarrhoea." | Not accepted. What is mentioned here is merely classic symptoms not the PROs as such. |
| 102 | 7 | Comment: Oedema is not associated with a defined endoscopic alteration. Assessment of erythema has an acceptable degree of | Accepted |

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| | | reproducibility<br><br>Proposed change (if any): delete oedema, insert erythema | |
| 104 | 7 | Comment on “histological findings (crypt distortion/abscess, ulceration, infiltration by mononuclear cells and neutrophils)”: assessment of neutrophils in biopsies will probably be the accepted criteria for histologic activity. | Accepted |
| 120-122 | 7 | Comment: Although it is true that according to the ECCO guideline, patients who have active disease despite prednisolone of up to 0.75 mg/kg/day over a period of 4 weeks are considered refractory to corticosteroids, this period of time is clearly too long. | Partly accepted. The section has been revised to give more general recommendations and refer to learned societies for specific definitions. |
| 124 | 7 | Comment: It is stated that "Patients are refractory to azathioprine/6-mercaptopurine if they continue to have active disease despite at least 3 months of treatment with a sufficient dose". It should be included 3-6 (instead of 3) month period, as it has already done in the CD document. | Partly accepted. The section has been revised to give more general recommendations and refer to learned societies for specific definitions. |
| 125 | 7 | Comment: The definition of remission in UC should also be clinical and endoscopic, rather than endoscopic with no or very mild symptoms | Not accepted. The present definition is maintained as complete absence of symptoms is likely to define patients with insignificant residual symptoms as not in remission. |
| 129-130 | 7 | Comment on: “(for the purpose of this guideline MH is defined as absence of macroscopic signs of active inflammation as judged by endoscopy)”: The category of complete absence of lesions should be contemplated, but it may be a less demanding definition and it could also be used in RCTs (e.g. a Mayo endoscopy subscore of 0-1, or a UCEIS of 0-1, if the latter is related to vascular pattern (no bleeding, no erosions)). Otherwise the proportion of patients achieving endoscopic remission in induction trials would be too | Partly accepted. In section 6.1.1.1. the option for a more liberal definition of endoscopic remission is included. |

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| | | low, and the outcome would be less meaningful. | |
| 178-179 | 7 | Comment: although in the introduction the guidelines also mention UCEIS, this score is not used in the rest of the document, e.g. definition of primary endpoint.<br><br>Proposed change (if any): a definition of MH according to UCEIS should be added | Not accepted. The guideline only mentions Mayo as an example. It cannot give definitions for all present and future instruments. |
| 193 | 7 | Comment: Secondary endpoints<br><br>Proposed change (if any): UC-related hospitalisation free survival should be considered as secondary endpoint | Partly accepted. The section has been amended to state that other secondary endpoints may be included provided adequately justified |
| 205 | 7 | Comment on histological normalisation: Disappearance of neutrophil infiltration may be a preferable definition. Complete normalization including restoration of mucosal architecture may not be reached. | Partly accepted. The text has been modified to state histological remission awaiting validated instruments to grade histological inflammation and formal definition of remission in histological terms. |
| 209 | 7 | Comment on Time to response: time to relapse should be added for withdrawal study designs | Partly accepted. The section has been amended to state that other secondary endpoints may be included provided adequately justified |
| 216 | 7 | Comment on “In patients who are steroid dependent, withdrawal of the steroids may be the objective”: This is problematic in induction studies and in particular for drugs with slow onset of action. The inclusion of this endpoint in induction studies should be considered on a case-by-case basis. | Partly accepted. The entire section has been revised |
| 217 | 7 | Comment: It is proposed that mild to moderate and moderate to severe UC have separate trials, but it should also be acknowledged that the definitions of mild and moderate are weak and poorly replicated | Accepted |
| 229-232 | 7 | Comment on pharmacokinetics: it should be investigated also according to disease severity | Not understood. |

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| | | Proposed change (if any): add “according to disease severity” | |
| 241 | 7 | Comment: The proposed duration of phase 2 dose finding studies at 6 -8 weeks is too short. Eight to 12 weeks would be more appropriate, particularly if endoscopic and histological changes are assessed | Accepted. However, the text already states that studies should not be shorter than 6-8 weeks, thus allowing for study duration as proposed. |
| 262 and 393 | 7 | Comment: As with Crohn’s disease most studies currently maintain steroid dosage at entry dose until the primary endpoint of active disease. This may be a prolonged steroid treatment period, but is designed to avoid the interference in therapeutic signal related to steroid withdrawal. Therefore, steroid withdrawal should be done early in the maintenance study | Partly accepted. Text has been revised accordingly. However, a recent induction study did implement steroid tapering systematically. |
| 275-277 | 7 | Comment: "a score of 6-12 in the clinical part of the Mayo score may be used as an inclusion criterion". However, the clinical (non-endoscopic) Mayo score can be 9 maximum.<br>Moreover, with regard to patient selection for induction of remission, shouldn’t rectal bleeding score at least 1 be included? | Partly accepted. The text suggests the use of the total Mayo score (with a maximum of 12). A requirement for a certain minimal inflammation secures objective inflammation. |
| 282 | 7 | Comment: "Shorter duration of disease has to be justified and care must be taken to avoid inclusion of patients with diarrhoea due to other causes e.g. infections and Crohn’s disease"<br><br>Proposed change (if any): delete "Crohn's disease", as this possibility is generally not ruled out in the short-term (3 months). | Accepted |
| 284 | 7 | Comment: Primary endpoints for active disease should be clinical and endoscopic remission, and not steroid free remission which is more appropriate for maintenance studies. | Partly accepted. Text has been modified to state that concomitant steroids may be acceptable for short term inductions studies. |
| 289-291 | 7 | Comment: that "clinical trials aiming at supporting a first line indication should always include comparison with the accepted first line treatment. Unless the study is aiming at demonstrating | Not accepted. One of the ways of securing assay sensitivity is adding a placebo arm (please refer to relevant ICH guideline. |

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| | | superiority against an existing treatment, it is critical that assay sensitivity can be demonstrated, ideally by adding a placebo arm". There seems to be a contradiction here (with the placebo inclusion/exclusion). | |
| 298 | 7 | Comment on: “it is advised that the established therapy is continued “. It should be mentioned “If safety is not compromised” | Not relevant as the text has been deleted. |
| 304 | 7 | Comment: It is pointed out that "However, the option of a 3-arm trial with placebo and an active comparator, where the latter would serve as an internal reference (not requiring formal non-inferiority) may be acceptable in certain circumstances". However, I think the inclusion of placebo here is not acceptable. | Partly accepted. Placebo may be ethically justifiable provided adequate rescue procedure are in place. Test has been amended to state that …”if ethically justifiable” |
| 322 | 7 | Comment on “TNF-experienced patients”.<br>Unless loss of response is related to immunogenicity: efficacy would not be likely, and safety seriously compromised, especially for IV drugs | This point is not relevant as the section has been revised. |
| 336 | 7 | Comment: It is supposed that patients with ongoing rectal bleeding should not be included in maintenance study. This issue should be clarified. | Partly accepted. Only patients who are in remission or have responded can be included in the maintenance trial. Response should be defined and justified according to the instruments used. The text has been modified to state this |
| 369 | 7 | Comment: "For a first line indication of maintenance of remission, the efficacy of maintenance therapy in this patient population should be determined by placebo-controlled trials if ethically justifiable". However, as 5-ASA have been demonstrated to be clearly effective, these drugs should be included as comparator.<br>Proposed change (if any): | This point is not relevant as the section has been revised. |
| 372 | 7 | Comment: comparators for the refractory population | Partly accepted. The text has been modified to give more general recommendations without specifically |

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| | | Proposed change (if any): add vedolizumab | rule one specific comparator in or out. |
| 371-373 | 7 | Comment on Choice of comparator.<br>A study with the active comparator mesalazine, powered for non-inferiority or superiority would be preferable, avoiding long term exposure to placebo | This point is not relevant as the section has been revised |
| 396-397 | 7 | Comment on "Usually tapering can be done with 2.5 to 5 mg/week in induction studies": this is too slow. 5 – 10 mg per week preferable (10 mg per week for doses > 20 mg/day) | Partly accepted. In principle, it is agreed. However, the more conservative regime is preferred in order to avoid relapse du to too aggressive tapering. |
| 401-405 | 7 | Comment: If topical treatment is allowed, endoscopic assessment should be done by colonoscopy | Partly accepted. The use of topical treatment has been removed. |
| 460 | 7 | Comment: Age, body weight, growth and sexual maturation should be taken into account for specification of the extrapolation plan. Moreover, body surface area should be added to this for younger children | Anthropometric parameters are basic criteria for any study in paediatric age, including extrapolation, specific GL update is not considered necessary |
| 518-519 | 7 | Comment: : the sentence is not clear.<br>Does it mean that in children placebo use should generally be used as an add-on to effective medication? If this is the meaning, ECCO supports such a statement and suggests that the standard for children in the placebo arm is to have access to use the investigational product if they relapse in addition to the conventional treatment they are on. | Placebo control is considered to be add-on to standard of care therapy. |
| 555-556 | 7 | Comment: Placebo is of high risk of colectomy, and significant risk of mortality. Corticosteroids should be the comparator for those not meeting the criteria of failure, and cyclosporine or infliximab should be comparators for corticosteroid-resistant acute severe ulcerative colitis patients. | Accepted |
| 563 | 7 | Comment: which definition of MH in case of pouchitis? | Not accepted. The guideline specifically states that there is lack of knowledge in this field. |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| General | 7 | Comment: When steroid are mentioned, it should not be taken only into account classical prednisolone, but also budesonide (MMX) and beclomethasone dipropionate (now mostly missing in study protocols) | Partly accepted. See previous response to same comment) |
| 211 | 8 | Comment: “Proportion in Steroid-free remission” is given as an example of steroid sparing effect. The co-primary endpoints, however, include “remission free of steroids”. It is not clear how these two differ, especially in maintenance trials (in induction trials where the primary endpoint allows a low dose if steroids it is not a problem).<br><br>Proposed change (if any): Either delete “such as: Proportion in steroid-free remission”, or provide a different example – one possibility is “such as: Proportion of patients using systemic steroid at baseline who achieve steroid-free remission”. | Partly accepted. The text has been amended to provide clarity. |
| 304-306 | 8 | Comment: When a non-inferiority trial is deemed impractical, a 3-arm trail with test drug (T), placebo (P) and an internal reference (R) is mentioned. Clearly, such a trial would need to establish the superiority of T versus P. It would be helpful if the agency could clarify if there is any expectation on the T:R and/or R:P comparisons. | Not accepted. It is already stated that formal non-inferiority between T and R is not requested. |
| 212 | 8 | Comment: Reduction in number of colectomies is an established secondary end point. Rates of hospitalization can also be used as an end point as there are cases that benefit from IV hydration and IV steroids and can be discharged prior to colectomy.<br><br>Proposed change (if any): Add hospitalization before colectomies | Partly accepted. The section has been amended to state that other secondary endpoints may be included provided adequately justified. |
| 312 | 8 | Comment: The document has considered treatment naive patients and anti-TNF refractory patients as comparators. | Partly accepted. The paragraph on comparators has been revised to give general recommendations as it is |

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| | | However, anti-integrin refractory patients must be considered as anti-integrin is increasingly used as a 1st line patient.<br><br>Proposed change (if any): Consider anti-integrin as a comparator in the treatment experienced sub-group. | not possible within the scope of a guideline to provide specific recommendations on all possible situations. |