28 June 2018
EMA/CHMP/261409/2017
Gastroenterology Drafting Group (GDG)

Overview of comments received on 'draft guideline on the development of new medicinal products for the treatment of Crohn's Disease' (EMA/CPMP/EWP/2284/99 Rev. 2)

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	Jordi Rimola MD PhD, IBD unit, Radiology Department, Hospital Clínic Barcelona, Catalonia-Spain
9	Takeda Development Centre Europe Limited, United Kingdom Takeda Pharmaceuticals Inc., United States

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Comment: The update of the Guideline on the development of new medicinal products for the treatment of Crohn's Disease 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.	No change necessary
1	Comment: 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 204 below).	On page 5, line 137 mucosal healing is clearly defined. On the same page remission is also clearly defined (line 137-139). These definitions are used trough out the text. Where ambiguity may exist, the text has been modified to comply with the definitions.
3	Comment: It is very important that to clarify the relationship between clinical remission and mucosal healing. Most patients who have a useful clinical response and some who go into remission will not have full mucosal healing. Because this document sees remission as full mucosal healing with few or no symptoms we lose most of the patients who would be eligible for maintenance of clinical remission trials. Page 5 lines 136 -138 and also page 10 lines 322 -323. The definition of remission needs to be changed to reflect clinical remission and endoscopic remission assessed separately. Until PROs are better established there will remain a problem with a definition of clinical remission, previously CDAI < 150 was widely used, just substituting mucosal healing does not solve this problem.	It is agreed that strict adherence to the dual requirements for remission may limit the number of patients who eligible for inclusion into the maintenance phase. Consequently, this requirement for inclusion into maintenance phase has been softened. However, it is not agreed that the definition of remission should be changed. A definition of clinical relevant control of the disease must include both symptoms and mucosal healing. As regards the definition of symptom control, please see below.
3	Comment: In studies of active disease it is traditional to clamp the steroid dose at the entry level through to the primary end point to avoid the instability caused by steroid withdrawal. P9 line 278. The document states that patients receiving steroids at entry should be	It is agreed that tapering of steroid during the induction phase may hamper evaluation of the effect of the drug. However, it is not considered in the patients' interest to be forced to uphold a relative high dose of steroids subjecting

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	off steroids at evaluation of efficacy. This should be the case for maintenance of remission, but is not realistic for induction of remission.	the patient to the harmful effect of a drug that does not work (if steroids worked the patient would not be included in the trial). The text has been modified in order to balance these two concerns.
3	Comment: Entry criteria by endoscopy must be corrected to allow isolated ileal disease, so the ileal sub score rather than the whole score needs to be used Page 9 line 282. It should be pointed out that such reliance on endoscopic evaluation excludes many patients, particularly those with strictures in whom the active inflammation may not be accessible to the endoscope.	Agreed
3	Post op patients assessment we all agree the absence of post op endoscopic recurrence is the gold standard. Page 10 line 343.	Accepted
4	Comment: EFPIA welcome the availability of these updated guidelines. The guidance is comprehensive and incorporates many of the recommendations made in the review and comment process on the Crohn's disease Concept Paper from 2014. However, we have 5 main areas of concern, where the EMA's proposed changes to the guidelines may have an adverse effect on the availability of new and potentially effective medications for Crohn's disease in the European Union. We view that this is contrary to the EMA's mission to "facilitate development and access to medicines", leading to "timely patient access to new medicines". **1.** The guidance 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 Crohn's disease" as described	No change necessary As regards point 1: It is not agreed that response is a valid primary endpoint. The clinical relevant aim of treatment is to bring the disease into remission. Thus, a new treatment is expected to achieve this goal, at least for a subset of patients. It is however, agreed that patients responding may benefit from continued treatment (beyond the induction phase) and may subsequently go into remission. Thus, patients showing a clinical response may be included into the maintenance phase. The guideline has been amended accordingly. As regards point 2: It is not the intention to request studies of longer duration that 12 months. A combined treatment length (induction and remission) of 12 months is however requested. In the maintenance phase of treatment, introduction of steroids/failure to wean off steroids as well as surgery are both unwanted from a patient perspective. Furthermore, the need for these treatment is a sure sign

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	in section 5 ' Indications/treatment goals'. A pre-defined 'Response' criteria can represent clinically meaningful "treatment of active Crohn's disease" and we would recommend EMA consider incorporating language into the guidance relating to 'Clinical Response' as not only a secondary endpoint but a primary endpoint for pivotal registration trials. **2.** 'Maintenance of remission/Prevention of relapse': primary endpoint of "maintenance of corticosteroid-free remission without surgery throughout at least 12 months" The Agency's suggested primary endpoint of "maintenance of corticosteroid-free remission without surgery throughout at least 12 months" is a laudable aspiration but is not a feasible endpoint for currently available medications. Mandating this endpoint in the EU will impose a requirement for very large maintenance cohorts, with treatment durations of longer than 12 months, making both the size and cost of maintenance studies unfeasible. **3.** Design of maintenance trial Including only remitters in the primary analysis makes the sample size needed in induction infeasible; the induction phase is not anticipated to be long enough to wean patients from steroids, and finally, many patients that are responders and not remitters at the end of induction achieve remission by the end of maintenance. The target population of a maintenance study should 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.	that the test drug lack efficacy. Thus, only maintenance of remission free of surgery and steroids, is a robust clinical endpoint. It is acknowledged that the current wording could be interpreted as a request for 12 months in remission without steroid and surgery (at all time points). As stated above, this is not the case. The text has been modified to avoid misinterpretation. As regards point 3: Agreed. The text has been changed to reflect this. As regards point 4: The requested clarification has been included. As regards point 5: *General EMA Guidance for the development of PROs (comparable to the FDA "Guidance for Industry Patient-Reported Outcome Measures: use in Medical Product Development to Support Labeling Claims" does not exist and applications are assessed on a case by case basis. The CHMP issues advice on methods with the aim moving towards qualification. The advice is based on the evaluation of the scientific rationale and on the preliminary data submitted to the Agency. Information on qualifications can be found under the following link: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004201.pdf* The text has been amended to suggest interim approach to assessment until PRO's have been fully validated.

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	4. The advocacy of a randomised withdrawal design poses a series of challenges; it is unclear in the guidance what sort of label is to be achieved if a more holistic 'treat through' design is adopted by sponsors, and what would be the label claim if a randomised withdrawal design is used. **5.** It would be helpful to understand if EMA recommends any specific guideline 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 Labelling Claims". Please recommend an interim approach to efficacy assessment that can be used prior to the validation of novel PROs.	
4	Comment: Highly desirable to have aligned positions of EMA and FDA on trial designs (e.g. induction/maintenance: rand. withdrawal vs. treat-through design; choice of comparator), handling of missing data, primary endpoint definitions(EMA suggests steroid-free remission as primary endpoint in pivotal trials (line #188) which is not requested by FDA and is appropriate only in patients who are on steroids at baseline); as well as on paediatric development program (e.g. extrapolation approach versus efficacy studies etc.);	Please see below
4	Comment: While we are supportive of EMA draft guidance, one topic that we believe the guidance should discuss in greater detail is symptomatic improvement in the absence of mucosal healing, especially in 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	Not agreed. It is agreed that in "hard to treat" patients (having failed several previous treatment modalities) mucosal healing rates in response to test drug are expected to be low. However, placebo healing rates are expected to be close to zero. Thus, demonstration of a statistically significant effect is considered realistic.

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	definitions of response have been altered, new drugs that offer incremental, but significant symptomatic 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 Crohn's disease occurred in small steps, yet these products were welcomed by patients and physicians because they represented additional effective treatment options even though they may not be considered "transformative" products.	
6	Comment: Lines 148-153: It is recommended to evaluate induction of remission and maintenance of remission in separate studies. In line with this, it is proposed to remove lines 328-337 (Trials combining …. 'maintenance of efficacy'.)(see textual comments below). <u>Motivation</u>: 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	Not agreed. The distinction between induction and maintenance is to some extent artificial. As for other chronic inflammatory conditions (e.g. rheumatoid arthritis) it is more in line with clinical practice (where patients are treated for extended periods of time) to request data on onset of action and number of patients in remission within 6-12 months. A treat through design may supplement evaluation of efficacy and also makes a direct comparison with standard treatment easier to implement and interpret. The text has been changes to state this.

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	and/or concomitant medication may unintentionally be provided to 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. In line with this, it is proposed to remove lines 328-337 (Trials combining …. 'maintenance of efficacy'.)(see textual comments below).	
6	Comment: Section 6.1.1. Primary endpoint It is agreed that symptomatic remission and endoscopic remission (i.e. mucosal healing) concern co-primary endpoints for both induction and maintenance treatment. 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. <u>Motivation</u>: On the one hand, achieving/maintaining remission free of steroids is considered primary endpoint (line 188) in proposed guideline. On the other hand, symptomatic remission and mucosal healing irrespective of steroid use are considered co-primary endpoints (line 195-196). Hence, definitions of (co-)primary endpoints need to be specified	It is agreed that the long-term goal should be remission (clinically and endoscopically) without the need for supplementary steroids. It is however also acknowledged that in short term studies (induction) it may not be feasible to taper steroids completely. To avoid the confounding effect of incomplete steroid tapering, steroids at a low and stable dose may be acceptable in short term studies. The text has been modified accordingly.

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	more clearly for appropriate implementation in clinical studies (see textual comment below). According to the international STRIDE consensus committee of experts in inflammatory bowel disease treatment of Crohn's disease should be targeted to achieve remission of clinical signs and symptoms AND endoscopic remission (Peyrin-Biroulet et al. 2015). 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. 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	Comment: Secondary endpoints In the absence of a validated patient-reported outcome with respect to the activity of Crohn's disease, total Crohn's Disease Activity Index (CDAI) scoring may be used as a secondary endpoint for clinical studies. <u>Motivation</u>: The Crohn's Disease Activity Index (CDAI) was used for many years to evaluate disease activity in Crohn's disease. Reliability and validity of CDAI scoring are however limited (Freeman 2008). Because of this, statements in proposed guideline that new patient-reported	Agreed. In the interim phase until PRO's have been fully validated CDAI score may be a useful secondary endpoint. The text has been modified accordingly.

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	outcomes should be developed and validated are agreed. This takes time. As CDAI scoring may provide some insight into disease activity during the study, total CDAI scoring may be used as a secondary endpoint in clinical studies with respect to Crohn's disease until more appropriate instruments to evaluate disease activity have been developed. This comment is in line with lines 280-283 indicating that in absence of fully validated patient-reported outcomes patients may be included based on total or subscale CDAI scores.	
6	Comment: Section 7.1 Pharmacology studies Pharmacodynamic effects in addition to pharmacokinetics and interactions are important with respect to treatment pharmacology in Crohn's disease (Quetglas et al. 2015), especially considering current absence of validated patient-reported outcomes. It should therefore be considered to provide some guidance with respect to the evaluation of pharmacodynamic effects (e.g. extent of metabolic conversion) in clinical studies.	Since it is impossible to foresee which targets are going to be addressed in the future, is very difficult to provide guidance on which pharmacodynamics studies to perform. No changes needed.
6	Comment: Section 8 Safety It is recommended to include a statement in the safety section that consideration should be given to potential treatment interactions, as these may alter clinical effects of study treatment.	A statement on interactions is already included in the pharmacology section. No changes needed.
6	Comment: Section 8.3.1. Paediatric patients It is recommended to evaluate effects of a new medicinal product for Crohn's disease first in adult patients. Provided both efficacy and safety of the new medicinal product are acceptable in adult patients, a paediatric study with a limited number of study patients (e.g. 30) should be conducted. Such a study has two major purposes: - confirmation of observed effects for adults in a paediatric patient	Partialy accepted, additional wording has been inserted into 8.3.1.3 and 8.3.1.5

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	population - evaluation of effects of the proposed medicinal product with respect to growth, maturation, and bone mass. Observation period should be sufficiently long for this evaluation. 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. A statement about the above should be included in revised guideline. Motivation: Impaired growth and sexual maturation may occur in paediatric patients with Crohn's disease (Malmborg & Hildebrand 2016). Peak bone mass, reached by late adolescence, is decreased in approximately half of children with Crohn's disease, especially in those malnourished (Bailey 1997). Failure to control inflammation and monitor linear growth and bone health may result in children not achieving their genetic growth potential and having an increased risk of fractures. Aforementioned risks with respect to impaired growth, sexual maturation and bone health (i.e. evaluation of osteopenia and osteoporosis) are not applicable (or at least much less likely) in adult compared to paediatric patients with Crohn's disease. Because of this, it is recommended to evaluate effects of new medication first in adult patients. 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	

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	population, and to (2) evaluate effects of proposed medicinal product with respect to growth and maturation and bone mass. 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. A statement about the above should be included in revised guideline.	
7	Comment: 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 Crohn's disease (CPMP/EWP/2284/99 Rev. 1)" 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. As general comment ECCO would like to point out that there seems some misunderstanding in the relationship between clinical remission and mucosal healing. Most Crohn's disease patients who have a	Please see response to stakeholder 3 As regards the use of CDAI as a secondary endpoint, please see response to stakeholder 6

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	useful clinical response and some who go into clinical remission will not have full MH (i.e. CDEIS/SES-CD=0). Because the current document considers remission as full MH with few or no symptoms, there is risk to lose most of the patients who would be eligible for maintenance of clinical remission trials (lines 136 -138 and 322 - 323). The definition of remission would need to be changed to reflect clinical remission and endoscopic remission, assessed separately. Until PROs are better established there will remain a problem with a definition of clinical remission (previously CDAI < 150 was widely used). Just substituting MH does not solve this problem.	
8	Comment: As a general comment, many endoscopic indexes are mentioned in the luminal crohn's disease section for grading the severity of the disease and endpoints. Magnetic Resonance Enterography (MRE) is just mentioned in the manuscript, as alternative to endoscopy, but there is no mention on MRE indexes. Below, I will suggest some specific information regarding this point. Also, MRE is suggested to be limited to small bowel assessment, but there are evidence indicating that MRE can be used for both small bowel and colonic evaluation after appropriate preparation of the colon (i.e. distension), reaching similar accuracy than endoscopy for detecting inflammatory lesions and response to medical treatment (Ajaj Gut 2007; Schreyer Gut 2005; Rimola Gut 2009; Rimola IBD 2011; Ordas I Gastroenterology 2014; Coimbra APT 2016; Boraschi Jpn J Radiol. 2016). The use of MRE instead of endoscopy may carry a number of advantages in clinical trials: - no incomplete evaluations for technical reasons (stenosis) or severity (that may happens around 80% of ileo-colonoscopies)	Partly accepted. It is agreed that a mentioning of the currently best validated instrument (MaRIA) is warranted. However, at the present time, this instrument has not been validated to an extent which would allow MRE/MaRia to be used as the sole instrument for assessing efficacy in phase 3 studies.

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	- evaluation of small bowel proximal to terminal ileum - Thus: higher rate of inclusion patients - Evaluation of peritoneum, allowing the detection of penetrating lesions or collections (potential exclusion criteria) Main limitation of MRE is low sensitivity for detecting mild inflammatory lesions that in clinical trials has minimal impact. Therefore, the use of MRE should be encouraged.	
9	Comment: In 2017, patients have several options for medical therapy with currently approved biologics and the oral kinase inhibitors which are on the horizon. Thus, we need to rethink patient selection by establishing new categories based on treatment exposure as well disease location. In general, small bowel disease is considered harder to treat than large bowel disease. In the document, line 114 defines steroid dependent CD and this category should remain the same. The Refractory CD cateogory on line 126 needs to be further elaborated into treatment sub-groups as follows- 1. Steroid refractory disease- usually these patients require hospitalization for antibiotics and surgery. Induction treatment with a biologic (anti TNF, anti integrin or anti-IL12/23) is recommended. 2. Bio Naïve- these are patients that may have been exposed to steroids, mesalamine derivates and immunosuppressants, but not to biologics. They could be either steroid responsive or steroid refractory. To date, in all clinical trials these patients show a higher efficacy of response to any given biologic in comparison to patients that are bio experienced.	In principle, it is agreed that the populations mentioned are relevant target population. However, any detailed description of all special populations refractory to one or the other treatment is bound to be outdated as soon as it is written. Instead of providing a detailed list of definitions of subgroups that is likely to be outdated very soon, it is considered more relevant to give general recommendations for defining treatment resistant groups. This has been provided.

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	3. Anti TNF refractory- this disease category is an area of opportunity as efficacy of anti-TNF is approximately 50%. In the USA, presence of active peri-anal disease meets criteria for the use of anti TNF biologic as a 1st line treatment even before steroids use. Therefore, this group needs to be highlighted, as there is opportunity for drug development. 4. Anti Integrin refractory- the efficacy of Entyvio is comparable to anti TNF and therefore, approximately 40-50% will not respond. This group is now relevant as Entyvio is used first line is select group of CD patients with co-morbidities that require a gut selective treatment approach. 5. Anti IL12/23 refractory- this is a new category and at the moment it's unclear in what context IL12/23 inhibition will be favoured as the first line agent. CD patients with co-existing psoriasis may be a potential indication as IL12/23 inhibition in psoriasis is highly effective. 6. Biologic treatment refractory CD- will be patients that have failed more than one class of biologic agents. Majority of these patients will have anti TNF exposure first followed by anti-integrin or anti IL12/23.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
103-106	1	Comment: The use of imaging techniques is not appropriate at this time for a patient population expected to have a mix of small intestinal disease and ileocolonic disease. There are no validated measures for magnetic resonance enterography to employ in clinical trials other than in an exploratory fashion. Proposed change (if any): 'Thus, in addition to signs and symptoms of active disease, patients included in clinical trials aiming at demonstrating efficacy in this situation should have evidence of active mucosal inflammation documented by recent endoscopy (ileocolonic disease) and/or imaging of the small intestine (e.g. ~~**magnetic resonance enterography (MRE) /**~~capsule endoscopy) (small intestinal disease only).'	Partly accepted. There are currently no fully validated MR scales for the entire gut. However, as stated in stakeholder 8, general comments, research in this field is ongoing and it would be unwise not include the use of MRE, if a validated scale becomes available. The text has been amended to reflect this.
114-125	1	Comment: Celgene would welcome a clarification from the Writing Group on the implications the classification of 'steroid dependent Crohn's Disease' patients would have for labelling or analysis purposes.	Partly accepted. In general, indications will reflect the population studied. As stated in response to general comments from stakeholder no 9, the guideline has been amended to include general remarks about possible target subpopulations. This revised paragraph also includes general information about the corresponding indications.
150-151	1	Comment: Celgene would like the Writing Group to include guidance on an acceptable indication text for treat-through design study. We would like to propose	Partly accepted. The requested information has been provided but does not match the proposal

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		'achieving and sustaining remission' as an example of indication that would be acceptable in the framework of a treat-through study. Proposed change (if any): 'While a "treat through" design may be acceptable the design of the study will have implications for the indications that can be claimed **(e.g. 'achieving and sustaining remission')**.'	
203-226	1	Comment: Celgene recommends retaining Crohn's Disease Activity Index (CDAI) as a secondary endpoint. Recently proposed patient-reported outcomes are not applicable to all situations and CDAI is still a globally-recognized important endpoint and would assist prescribers with comparison against historical data. Proposed change (if any): 'Secondary endpoints • **Crohn's Disease Activity Index (CDAI)**'	Accepted
204	1	Comment: There is currently no literature or data showing precedence of the requirement to meet both mucosal healing and symptomatic remission in each individual patient 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. Proposed change (if any): 'Secondary endpoints	Not accepted. There is general agreement (e.g. STRIDE criteria: The American Journal of Gastroenterology 110, 1324-1338 (September 2015)) that the therapeutic target in CD is symptomatic and endoscopic remission. Thus, fraction of individual patients achieving both these goals is indeed a relevant secondary endpoint.

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		• ~~**Individual patients achieving both MH and symptomatic remission'**~~	
210-211	1	Comment: There is currently no data demonstrating that patients with Crohn's disease who achieve histologic remission fare better than those who do not. This is true for ulcerative colitis patients, but not for Crohn's disease patients. The definitions of remission of both SES-CD and CDEIS scores have not been validated prospectively as well as in patient populations after surgery. This proposed endpoint is unreasonable at this time. Proposed change (if any): • 'Alternative definition of remission based on the primary endpoint with the additional requirement of normalisation of CRP and/or calprotectin as well as histological normalization • ~~**Histological evaluation of mucosal inflammation, including number of patients achieving histological normalisation**~~'	Not accepted. Although not fully validated as prognostic marker this endpoint is of interest in order to get a full description of the potential of the drug. It is acceptable as a secondary endpoint.
212-214	1	Comment: Celgene would like the Writing Group to include additional suggestions for instruments to evaluate symptoms and inflammation. The below suggestion is based on data collected in the SONIC Phase III clinical study of biologic and immunomodulatory naïve patients in Crohn's disease. Proposed change (if any):	Accepted

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		• 'Response, which should be defined according to the instruments used for evaluating symptoms and inflammation, respectively. For example, a decrease in CDEIS of >5 points combined with a decrease of >2 points on a 5 point scale evaluating symptoms**; or 25%/50% decrease from baseline in the endoscopic score as a response**'	
221-222	1	Comment: The recommended stratified randomisation according to disease activity (i.e. mild, moderate and severe) is not a specific definition. Celgene would welcome other suggestions for this classification by the Writing Group, such as the SES-CD score or the number of segments involved. Proposed change (if any): 'It is recommended to use a stratified randomisation according to**, for example, an SES-CD score above or below 12, or the number of segments involved** ~~**disease activity as judged by mucosal inflammation, e.g. mild, moderate and severe**~~.'	Accepted
258-269	1	Comment: Celgene understands the aim of the Agency to encourage the maintenance of patients off of steroids as a goal of remission studies. However, the design of studies for induction of remission as stated in this paragraph is confusing. Subjects should not be tapered off of any concomitant medication prior to endoscopy, as this might confound the comparison to placebo or active. Celgene would welcome clarifications from the Writing Group on this aspect.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any):	
276	1	Comment: Celgene agrees the use of histological examination makes sense for patients entering a trial. However, it is unreasonable to conduct histological examination on all patients at this time. It is not consistent with current clinical trials practice to include elements of histology as a requirement. It is unclear how histological examination should be used. Celgene would welcome a clarification from the Writing Group on the expectation to conduct histological examination in Crohn's disease patients. If this is just for documentation purposes, this should be clearly addressed in a separate statement and should not be put at the same level as endoscopy examination or radiologic imaging. Proposed change (if any): 'Degree and extent of mucosal inflammation should be documented by recent visualisation of the gastrointestinal tract, by endoscopic examination and/or radiologic imaging studies (MRE is only suitable for small intestinal disease that cannot be evaluated by colonoscopy) ~~**and histological examination**~~.'	Not accepted. As stated in previous response to stakeholder 1, histologic evaluation is an important element in describing the full potential of the drug. In order to make this evaluation possible histology at entry should be evaluated.
307-308	1	Comment: Celgene would like to propose a softer language in relation to the recommendation for a comparison with an anti-TNF compound. This should be limited to patients who are naïve to anti-TNF inhibitors. Most trials in Crohn's disease study the moderate to severe population, and would fall into the	Partly accepted. Comparison with a TNF inhibitor is only relevant in TNF-inhibitor naïve patients. In these patients, a comparison with a TNF-inhibitor is recommended. The text has been revised.

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		category of refractory as defined earlier. We would like to limit the suggestion to use an anti-TNF compound as a comparator for this population. Proposed change (if any): 'For patients with severe, steroid and immunosuppressive refractory CD **who are naïve to anti-TNF inhibitors**, a comparison with an anti-TNF compound ~~**is recommended**~~ **should be considered**.'	
Lines 309-361 (section 7.2.2.2. on Maintenance of remission/ Prevention of relapse)	1	Comment: Clarification and advice on suitable treat-through design are needed throughout this section on maintenance of remission and prevention of relapse.	Accepted
328-332	1	Comment: 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	Not accepted. For the indication "maintenance of remission" the primary analysis should be patients entering this part in symptomatic remission (otherwise there will be no remission to maintain).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		efficient recruitment of patients into the maintenance study since it is expected fewer patients will achieve remission than response in induction. 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. 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.'	
343-344	1	Comment: Celgene would suggest that the primary endpoint for maintenance studies should be maintenance of steroid-free remission without surgery throughout 3 months instead of 12 months which seems very challenging. Proposed change (if any): 'It is recommended that the primary end-point should be the maintenance of steroid-free remission without surgery throughout **3 months** ~~**at least 12 months**~~.'	Accepted.
407-408	1	Comment: The guideline should specifically state that the cancer risk in IBD paediatric patients may last for	Partly accepted, lifetime cancer risk but in IND in general

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		the whole life of the patient. In addition, this sentence should focus on the risks of Crohn's disease patients' only. Proposed change (if any): 'Subsequently children have a ~~**higher**~~ **lifetime** cancer risk, longer duration of disease, severity or extension of disease compared with adult-onset **CD** ~~**IBD**~~.'	
416-417	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. **Age definition is mentioned in ICH E11, but the cut of age for patients to be included into the adults study should still be justified by the applicant, depending on the products profile**
438	1	Comment: The verification of whether a comprehensive amount of data has already been collected should be done in adults with Crohn's disease, and not ulcerative colitis. Proposed change (if any): • 'Whether a comprehensive amount of data has already been collected in adults with **CD** ~~**UC**~~'	Accepted
454-457	1	Comment: Celgene would like to ask for clarification on the following sentence and to suggest the below rewording. Proposed change (if any): 'The results of this covariate analysis can be used in case a certain exposure (AUC or Ctrough) for instance	Partialy accepted. Sentence has been clarified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		similar to adults is aimed for, to identify whether~~,~~ 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.'	
475-478	1	Comment: Celgene would like to ask for clarification on whether a distinction is made between adolescents and paediatric patients – if adolescents are to be included in adult studies, shouldn't the same PRO endpoints be used for adolescents?	Accepted
52+53	2	Comment: Percentages should add up to 100%.	Accepted
55	2	Comment: Mortality is only increased in severe disease – this should be stated.	Accepted
67	2	Comment: *"Perianal manifestations are common":* common is unspecific – acc to epidemiology data it should be 10-15%.	Accepted
105	2	Comment: "*recent endoscopy*": a clarification what "recent" means would be helpful. The endoscopy must have been performed after a possible resection because this changes the anatomic distribution and possible presence of lesions.	Accepted.
132	2	Comment: "if they do not respond to a sufficient dose": need to specify the dose for azathioprine and 6-MP separately.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
190-195	2	Comment: Defining endocopic remission as a SES-CD or CDEIS score of 0 is not realistic. Only very few patients will reach that endpoint. If then this is co-primary with symptomatic remission off steroids less than 5-10% of the patients will achieve this with active treatment and the sample sizes needed for studies will increase hugely.	Accepted
200-202	2	Comment: It is impossible to taper and discontinue steroids during an induction study with the endpoint at e.g. 8 weeks.	Accepted
222	2	Comment: How to define mild, moderate and severe?	Accepted.
215-216	2	Comment: Time to remission and time to response only works with symptom scores as repeat endoscopies/imaging of small intestine (others than at baseline and primary endpoint) are not feasible. Proposed change (if any): • Time to remission (symptom scores or biomarkers only) • **Time to response (symptom scores or biomarkers only)**	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
221-222	**2**	Comment: Stratification according to mucosal inflammation (e.g. mild, moderate, severe) is recommended. **Categorisation of disease severity according to mucosal inflammation is neither an established nor validated procedure.**	Not accepted. Please see response to stakeholder no 1
249-251	**2**	Comment: Addition of numbering could improve the readability of the enumeration at the beginning of the sentence. Proposed change: 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 (please see Guideline on missing data).	Accepted.
260	2	Comment: The timeframes for control of active disease in UC are **much** shorter – maybe a justification would help.	Not accepted. This belongs in the UC guideline.
298	2	Comment: Placebo control would only be accepted by ECs for trials in mild disease or as part of an add-on design.	Not accepted. No change necessary. The text is sufficiently flexible to allow omission of placebo (if ethically unjustifiable).
304-306	2	Comment: “documentation of the insufficient response”: clarification how this has to be documented would be helpful.	Partly accepted. It is acknowledged that true documentation of insufficient response (previous medical records) may be difficult to supply. Where such cannot be obtained, written confirmation form the investigator that previous treatments were insufficient, could be acceptable.
323	2	Comment: It is not feasible to include only patients with complete mucosal healing in maintenance studies	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		especially with such criteria of endoscopic remission.	
332	2	Comment: The primary endpoint of maintenance of remission in remitters only again decreases the proportion of patients who will achieve this endpoint and will lead to a huge increase in patient numbers needed.	Not accepted. Please refer to previous response.
261	2	Comment: Follow-up period off-treatment to see if patients in remission at end of treatment remain in remission. In clinical practice only mild patients discontinue medical therapy after induction of remission. Proposed change: “An appropriate follow-up period off therapy is recommended in mild patients 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.”	Partly accepted. It I s agreed that discontinuing treatment is not a standard approach. Thus, the requirement has been removed.
366	2	Comment: *“and to limit the need for surgical interventions”:* surgical intervention can be the permanent solution and therefore the preferred option. The text does not reflect this.	Not accepted. Apart from relief of symptoms, maintaining the integrity and function of the GI tract is the ultimate goal of treatment. It is acknowledged that for some patients (ileocoecal disease) surgery may provide long term relief better that the available medical options. But this is merely a testimony to the inadequacy of the available medical therapies. Not an argument for the superiority of surgery.
11	3	Comment: Keywords: I suggest adding: Inflammatory bowel disease, and CDAI.	Partly accepted. IBD has been added. CDAI is obsolete.
62	3	Comment: stricturing or fistulizing disease.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
71	3	Comment: delete "antibiotics (for colonic disease)", as these drugs have no role in the treatment of CD.	Accepted
73	3	Comment: Nutritional support also has a role as primary therapy... add: in children.	Accepted
98	3	Comment: Document seems to be focusing on luminal disease only, perhaps better split up into luminal disease and fistulizing disease	Partly accepted. The guideline already has a section on fistulising disease. No change necessary.
131	3	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.	Not accepted. The ECCO definition is only an example. Other definitions may be used. No change necessary.
136	3	Comment: Suggest to split this up in clinical remission and endoscopic endpoints.	Accepted
138	3	Comment: for the purpose of this guideline MH is defined as absence of macroscopic signs of active inflammation as determined by endoscopy... Consider stating absence of ulcers instead of absence of active inflammation. The absence of macroscopic signs of active inflammation is probably a too hard endpoint, probably better to limit it to absence of ulcers	Accepted
203	3	Comment: include CD related hospitalization free survival	Partly accepted. The suggested specific secondary endpoint has not been included. However, it has been stated that additional secondary endpoints may be included if adequately justified.
278	3	Comment: It is stated that "In patients receiving steroids at entry, the medication should be tapered before evaluation of efficacy", but this should not be the case in most RCTs.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
282	3	Comment: It is pointed out that "patients included must also have a certain minimal level of mucosal inflammation (e.g. a score >8 when using CDEIS or a score >6 when using SES-CD)". However, recent RCTs allow to include patients with only ileal involvement, in which case the SES-CD should be corrected to consider only this location.	Accepted
295	3	Comment: It is stated that "clinical trials aiming at supporting a first line indication should always include comparison with the accepted first line treatment. However, later on it is pointed out that: 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).	Partly accepted. There is no contradiction. The placebo arm should be added in addition to the active comparator (i.e. the accepted first line treatment). In this 3-arm study, the purpose of the placebo arm is to demonstrate assay sensitivity in a non-inferiority comparison between test drug and active comparator. The guideline has been amended to make this clearer.
322	3	Comment: It is pointed out that "for inclusion into maintenance studies patients are expected to have MH (e.g. SES-CD, CDAIS of 0)". However, this 0 score is not necessary (nor feasible in most of the cases).	Accepted
343	3	Comment: For operated patients, even more important than "clinical post-operative recurrence" is "endoscopic" recurrence, as it is more objective, more reliable, and has a clear prognostic value for predicting clinical recurrence.	Accepted
101-102	4	Comment: It would be helpful if the EMA could provide advice about the appropriate population in which to study agents (such as direct mucosal healing agents) that are intended to improve MH but not necessarily have a direct anti-inflammatory effect and are not	Not accepted. Today no such compounds have been developed. It is outside the scope of the guideline to speculate on choice of design in this speculative situation.

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		necessarily intended to alleviate symptoms. One could envision a situation, say, where an agent may be added to background therapy in patients who are in clinical remission but have residual endoscopic evidence of disease and a clear regulatory pathway for that would be helpful.	
103-106 and 109-110	4	Comment: Imaging modalities are used in clinical practice. However, imaging criteria to confirm mucosal inflammation have not been robustly validated for use in clinical trials (see point relating to lines 109-110, below). Proposed change (if any): Suggest clearly discriminating between diagnostic modalities that are used in clinical practice and those that are validated, or semi-validated, and would be acceptable to the agency as instruments to determine eligibility criteria for a clinical trial.	Accepted
109-110	4	Comment: Histologic evaluation prior to inclusion can be used to confirm the differential diagnosis of CD. However, histologic disease activity criteria have not been developed or validated, and therefore cannot yet be implemented as an eligibility tool, or be used in the randomization/ stratification of subjects, or to support statistical assumptions (e.g. sample size and power) for a study.	Partly accepted. The remarks made by the stakeholder regarding the limitations of histology are accepted. However, the guideline does not use histology as suggested. Thus, no change is necessary.
112-113	4	Comment: Previous programs have required moderate to severe CD patients to have a minimum of at least 3 months elapse between diagnosis and enrolment into clinical trials to establish disease activity in the setting	Accepted. But the guideline does not claim any of these things. No change necessary

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		of adequate treatment. Clarification is requested of the statement: "Patients with evidence of **active inflammation** over a period of 3 to 6 months …". What is meant by 'inflammation' in this context; is this mucosal inflammation as established by repeated endoscopies/MREs and histological assessments or elevated CRP and/or fecal calprotectin; or clinical signs and symptoms of active disease? The agency should clarify if a demonstration of disease activity is required at 1 timepoint or at multiple timepoints for inclusion in a study.	
112-113	4	Comment: The classification of patients into "steroid-dependent" or "refractory" categories eliminates a regulatory pathway for treatments focused on mucosal healing or those for patients who have milder, earlier disease. It is not necessarily the case that all new drugs must be positioned after steroids and/or IMMs, depending on anticipated safety and efficacy profiles.	Not accepted. The guideline does not preclude pursuing a first line indication (i.e. before steroids). It merely requests that any new first line treatment must be compared to current first line treatment. No change necessary.
114-115	4	Comments: Proposed change: "… Patients who respond to steroids but whose disease flares on tapering (precluding steroid withdrawal) **and have a relapse within 3 months of stopping steroids** are classified as being steroid dependent."	Accepted
119-120	4	Comments: Tapering schedules may be difficult to standardize for corticosteroids other than prednisone-like steroids and budesonide.	Not accepted. The definition cited is just an example. Other definitions may be used provided that the choice is adequately justified.
114-135	4	Comments: The categories outlined do not provide an	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		allowance for patients who are unable to tolerate steroids/IMMs or who have contraindications to such therapies. Proposed change: Line 135. Add statement to indicate that other classes of patients, who may benefit from novel therapies, exist. E.g. patients who are intolerant of conventional therapies or have contraindications to same.	
131	4	Comments: Replace '0.75 mg/kg/day' with '1mg/kg/day', as per ECCO 2016 guidelines	Accepted
133-135	4	Comment: The guidance describes patients as TNF-refractory if they make no initial response to appropriate doses /duration of anti-TNF therapy. The guidance does not consider patients who initially respond, but subsequently lose response (i.e. secondary non-responders) nor does the guidance address intolerance to therapy. Further, multiple biologic therapies with alternative mechanisms of action other than those targeting TNF are now approved for the treatment of CD (e.g. vedolizumab and ustekinumab), but are not addressed in the guidance. Proposed change: Expand definitions of refractoriness to available biologic therapies to include secondary loss of response and intolerance. Expand guidance to include biologics other than anti-TNFs.	Partly accepted. Please refer to response to general comments by stakeholder no 9.
133-135	4	Comment: Please add context to "refractory to anti-	Partly accepted. Refractoriness (primary non-response) should

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		TNF therapy" seems to refer specifically to "primary non-response to anti-TNF therapy". Because refractory patients may have had either/both primary or secondary non-response, we recommend additional clarity in this section. Proposed change (if any):"Patients are refractory to anti-TNF therapy if they make no initial response to ~~appropriate doses/duration of anti-TNF therapy~~ any given anti-TNF biologic (primary non-response) or if they have lost previous efficacy from a given anti-TNF biologic (secondary non-response)".	not be confused with loss of response (secondary non-response). Mechanisms of non-response differ and response to subsequent treatment differs. Thus, they should be clearly distinguished. The text has been revised accordingly.
136	4	Comment: The definition of "CD in remission" appears to actually describe a state of "deep remission." There may be patients who have MH and not clinical remission, or vice versa. Proposed change: The guidance should discriminate clearly between different categories of remission, e.g. clinical remission, endoscopic mucosal healing and "deep" remission, which is a combination of clinical remission and endoscopic mucosal healing. Furthermore, the agency could consider specifying if they envisage an alternative pathway towards approval for a medication that is intended to maintain remission in patients currently in remission, or to achieve additional endpoints such as endoscopic or histological mucosal healing in patients who are in clinical remission with evidence of mucosal	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		inflammation.	
137	4	Comment: Absence of macroscopic signs of active inflammation is a poor definition of mucosal healing. It suffers from a lack of specificity and is also very restrictive. For example, does mucosal erythema or a loss of normal vascular pattern count as “active inflammation”? Proposed change (if any): Consider changing this definition to an “absence of ulceration” on endoscopy, which is consistent with previous clinical trials, and specify the CDEIS or SES-CD cut-offs required for inclusion, achievement of endoscopic response and remission and mucosal healing.	Accepted
	4	Comment: Based on the phase 3 data published for ustekinumab in CD, the effect size expected for mucosal healing may be very small and sample size needed to prove efficacy using this measure may be prohibitive. A more suitable endpoint for this could be ‘endoscopic response’, defined as a percent improvement (i.e. 25%) in SES-CD	Not accepted. The lack of efficacy of one drug should not prevent setting clinically relevant goals for future treatments.
143-144	4	Comment: “In order to obtain an indication for “treatment of active Crohn’s disease”, efficacy in both “induction of remission” as well as “maintenance of remission” should be demonstrated.” This statement is confusing, as it suggests that only success in an induction->re-randomization->maintenance study design program will lead to an indication of “treatment of active Crohn’s disease”. It suggests that a treat-through study design that demonstrates efficacy in	Partly accepted. “Treat through” studies” and “induction-re-randomisation-maintenance” studies both have strengths and weaknesses. The text has been re-written to provide the possibility of both designs.

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		both induction of remission and sustaining remission is not a suitable design to obtain the label claim of "treatment of active Crohn's disease". This should be clarified. Proposed change (if any): New sentence at line 144. "A treat-through study design showing efficacy in both "induction of remission" and "sustained remission" may be suitable to obtain an indication for "treatment of active Crohn's disease". Please clarify the label claims that a treat-through design would be likely to support, to make consistent with FDA guidance.	
143-147	4	Comment: Text in lines 143-147 does not include text regarding induction/maintenance of a clinical response 'Achieving/maintaining remission free of steroids is an appropriate primary end-point. In patients receiving systemic steroids these should be tapered according to predefined schedules. For induction studies of short duration requiring early evaluation of efficacy a low dose of steroids may be acceptable provided that the dose is clearly justified and pre-specified.' The agency should specify that clinical response remains an appropriate endpoint in CD clinical trials, as shown in italics below. This guidance suggests that it does not. Proposed change (if any): Achieving/maintaining remission free of steroids is an appropriate primary	Not accepted. Induction/maintenance of response is not considered a valid primary endpoint. It may be a relevant secondary endpoint.

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		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.	
148-153	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. 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	Accepted. The guideline has been revised to allow a treat trough design.

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		weeks). If sufficient initial benefit is achieved, patients will continue to be maintained on that treatment for a longer time, with ongoing observation to ensure there is sustained benefit. Enforcement of a strict induction and maintenance study paradigm (i.e. induction followed by randomization to active drug maintenance or withdrawal to placebo) without consideration of the time to achieve optimal PKPD effects will limit our ability to evaluate the true efficacy potential of a given MOA, because patients who “are not induced” into response will not continue into the randomized maintenance trial. Historically, biologic trials have studied induction efficacy at time points ranging from 2 weeks to 12 weeks; and most of these trials have reported that a substantial proportion of patients may achieve a delayed response to induction (i.e. the non-randomized population in the randomized withdrawal maintenance study). Thus, a treat-through design, which evaluates efficacy from a population perspective, would provide a much more accurate assessment of the real efficacy potential of a MOA, both short-term and long-term. Additional comments regarding the appropriateness of treat-through vs. randomized withdrawal maintenance studies are provided in response to Lines 328-341.	
162-165	4	Not all therapeutic drugs for the treatment of IBD are	Not accepted. Inflammation is at the core of the pathogenesis

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		necessarily targeting the inflammatory process. The wording in this paragraph suggests no regulatory pathway for those approaches.	of inflammatory bowel disease such as Crohn's disease. A drug not targeting inflammation is not considered a treatment of Crohn's disease but merely symptomatic treatment (pain/diarrhoea). It is outside the scope of this guideline to provide guidance on anti-diarrhoea compounds/analgesics.
166-171	4	Comment: We advocate the continued use of the CDAI until new PRO endpoints/criteria have been validated. Furthermore, the continued collection of the CDAI 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 CDAI. Proposed change: Delete or preface the statement in line 171 which discourages the use of the CDAI as a primary endpoint in future studies with clarification of when use of the CDAI might be appropriately acknowledged.	Partly accepted. It is acknowledged that in the interim period until fully validated PRO's are developed, inclusion of CDAI may be necessary for comparison with historic data. However, CDAI is not specific to Crohn's disease symptoms induced by inflammation (e.g. CDAI score may be high in patients with IBS like symptoms but without any active inflammation). Thus, CDAI cannot be a primary endpoint. It may be acceptable as a secondary endpoint.
172-176	4	Comment: The current guidance text states: 'Instead of a combined index such as CDAI, signs and symptoms and inflammation should be evaluated independently. A significant effect on both aspects of the disease is required (co primary endpoints). Symptomatic relief should be evaluated by patient related outcomes (PRO) (e.g. number of loose stools and abdominal pain). This guideline therefore recommends the further development and validation of PRO instruments for the use as primary outcome parameter in clinical trials in CD. Such an instrument	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		should include the clinically important signs and symptoms of CD, e.g. abdominal pain and diarrhoea. An instrument to be used as primary outcome measure in pivotal clinical trials in CD should be completely and rigorously validated.' This statement should be updated with consistent language on suggested components of the PRO and to correct an error in the term PRO. Proposed change (if any): Symptomatic relief should be evaluated by patient reported outcomes (PRO) (e.g. Stool frequency and abdominal pain). This guideline therefore recommends the further development and validation of well-defined and reliable PRO instruments that measure clinically important signs and symptoms of CD for the use as primary outcome parameter in clinical trials in CD. Such an instrument should include the clinically important signs and symptoms of CD *(e.g.* ~~abdominal pain and diarrhoea~~ Stool frequency and abdominal pain). An instrument to be used as primary outcome measure in pivotal clinical trials in CD should be completely and rigorously validated.'	
172-180	4	Comment: Please recommend an interim approach to efficacy assessment that can be used prior to the validation of novel PROs. FDA guidance currently suggests that investigators use a 2-component PRO (pain and stool frequency) with an assessment of the endoscopic appearance of the mucosa. This appears to be included in lines 280-288, but it	Accepted

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		would be worthwhile to also include this here for clarity. Proposed change (if any): Please recommend interim efficacy assessment criteria that would be acceptable to the Agency.	
173	4	The strict requirement for co-primary endpoints (PRO plus endoscopy) may not necessarily be applied to all patient populations or all categories of therapy. Given the uncertainty of the benefit of treating to mucosal healing, it is suggested that this be a required ranked secondary endpoint (instead of a co-primary endpoint).	Not accepted. Endoscopic severity predicts long-term prognosis in Crohn's disease patients with clinical remission. Thus, mucosal healing is a relevant co-primary endpoint.
179-180	4	Requiring response in terms of “all parameters” is not possible in the case of patients who are enrolled with isolated SF or isolated AP (which is possible). Requiring all patients to enrol with pain and elevated SF reduces the generalizability of the population studied, but would be a necessity of response definitions require improvements in both parameters. A response definition of improvement in at least one parameter and no worsening in the other parameter seems more reasonable.	Accepted
181 – 183	4	Comment: The guidance recommends a validated scale such as CDEIS or SES-CD as endpoint for mucosal healing. There is no guidance on the endpoint if MRE is used and we are not aware of a validated MRE endpoint. There are studies comparing an endoscopic index with an MRE-based index that found a statistically significant correlation (Gastroenterology	Accepted

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		146: 374), but the correlation is really weak (r = 0.51 for magnitude of change). Proposed change (if any): Please recommend an approach to MRE that would be acceptable to the agency. Add the following sentence to the line 185: "It should be noted that the assessment of small bowel mucosal inflammation using MRE is empiric, and there are no validated tools to grade intestinal inflammation using this imaging modality.	
187-202	4	Comment: Please provide further guidance on how to re-randomise to maintenance with symptomatic remission and MH Endpoints.	Accepted
188	4	Achieving/maintaining symptomatic remission free of steroids Comment: Corticosteroid-free remission is too stringent to be used as a primary endpoint and is technically unachievable at the end of the induction period (in induction tapering is usually not encouraged to safeguard patients and minimize confounders for efficacy assessment). It would be challenging to recruit for a study focussing on patients who are steroid dependent, within a reasonable timeframe. Analysis of this EP will heavily be confounded by the proportion of patients with steroid use at baseline. This primary EP would basically exclude patients who are not on steroids at baseline, which make up for 50-80% of phase 3 trial populations.	Accepted

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		Prescribers will need comparable endpoint information to select the right treatment for patients based on (indirect) comparisons of various drugs. Thus, comparable endpoints should be applied in the future as in the past to support clinicians in their decision making. The suggested endpoint of corticosteroid-free remission may be challenging to meet in this difficult-to-treat sub-group and require an unfeasibly large study to have sufficient power to meet this endpoint. Clinical response would be a more feasible primary endpoint in these patients, with corticosteroid-free clinical response as the first secondary endpoint. Clinicians understand the difference between these endpoints and the implication of achieving each of these endpoints on a per-patient basis. Proposed change (if any): Achieving/maintaining symptomatic remission free of steroids is an appropriate ~~primary~~ endpoint.	
190-1	4	Comment: The example is not fully clear? Do “no” or “mild” symptoms represent 2 out of 5 ranks on an ordinal scale?	Accepted
190-191	4	Comment: The guidance mentions a 5-point scale for evaluating symptoms. Does EMA prefer a 5-point scale for evaluating CD symptom? The current CDAI used a 4-point scale (0-3) for rating abdominal pain. Literature suggests that a 0-10 numerical rating scale is also appropriate for recording symptoms like pain.	Not accepted. The 5-point scale is merely an example. In order not to imply any preference, this example has been removed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
190-191	4	Comment: Remission of signs and symptoms is a high bar for success – although the Agency define remission as “no” or “mild” symptoms. While advice is provided on a 5-point scale currently in the guidance document, the 11-point numeric rating scale (0-10) is often the preferred measurement scale in modern test theory and science, and most new PROs are developed using such a rating scale (to enhance sensitivity, normality of distribution, reproducibility and provide sufficient response options for patients). Proposed change: can the Agency provide advice on their definition of remission on 11-point numeric scale	Not accepted. Please response to the above comment. Advice on the exact definition of remission must await full validation of the PRO.
192	4	Comment: Achieving/maintaining mucosal healing as primary EP is a very high aim for a 6-12 week induction trial, a less strict endpoint should be accepted in the induction setting (e.g. endosc. response);	Accepted
192-193	4	Comment: This sentence states that MH should be “considered” to be a co-primary endpoint. This wording is appreciated, but contradicts the wording on line 173.	Accepted. The text has been modified in order to provide clarity.
Line 200	4	Comment: Steroid tapering and steroid free remission should not be requested in induction trials as this will confound endpoint assessment and increase the failure rate as compared to patients in stable remission during maintenance. This should be clarified to confirm that a tapering schedule is not mandated during the induction phase of the study.	Accepted
200-201	4	Comment: It is not clear what “a low dose of steroids may be acceptable” refers to. Inclusion criteria?	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Steroid-free remission endpoints? Flexibility should be given to sponsors for whether "steroid –free" must always comprise a remission definition, and accepts that labelling will reflect the endpoint chosen for the study.	
200-201	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 exclude patients who have higher disease activity and therefore limit the ability to understand the effectiveness and safety of the therapy in this more severe population (Ha et al, Clinical Gastroenterology and Hepatology, 2012, 12:1002-1007). Proposed change: Delete reference to "low dose" and restate as "….~~low dose of~~ concomitant steroids ~~may~~ would be acceptable provided that the dose is clearly justified and pre-specified."	Accepted
205	4	Comment: The secondary endpoint suggested in line 205 "Remission defined slightly more differently than primary endpoint" is ambiguous.	Accepted

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		Proposed change (if any): Please further clarify this statement.	
210-211	4	Comment: There are no standard criteria of histological normalization. Additional histological datasets are required to define histological normalization. Proposed change: Evaluation of histological improvement should be included as an exploratory endpoint to assess CD activity and treatment efficacy.	Not accepted. A distinction between exploratory and other secondary endpoint is not necessary. They are all secondary endpoints.
212-214	4	Comment: Does a decrease of >2 points on a 5 point scale need to be validated for evaluating a specific symptom or is it a universal criteria for any symptoms? “a decrease in CDEIS of >5 points combined with a decrease of >2 points on a 5 point scale evaluating symptoms” Use of a hypothetical 5-point scale is confusing and ambiguous. This example should be removed. In addition, the agency should be more specific in the use of the word “inflammation”. Please clarify whether this relates to endoscopic evidence of mucosal inflammation, histological evidence of mucosal inflammation or evidence of inflammation as determined by another modality, such as a blood or stool test.	Accepted
218	4	Comment: Changes in general health related quality of life like SF-36 can be observed in an induction study of	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		8-12 weeks. Proposed change: Propose to include generic HRQL as optional assessments in an induction study.	
219	4	Comment: Steroid-free remission is listed as a secondary endpoint (which we believe is the appropriate place for this endpoint in most trials) but this contradicts lines 188-189.	Accepted
219	4	Comment: Please clarify how *steroid sparring effect such as: Proportion in steroid free remission* is different from the primary endpoint.	Accepted
No line mentioned	4	Comment: Would discontinuation of steroids or a quantitative reduction of steroid dose regardless of symptomatic/endoscopic endpoints be acceptable as secondary endpoints, too?	No.
221-222	4	Comment: The statement, 'It is recommended to use a stratified randomisation according to disease activity as judged by mucosal inflammation, e.g. mild, moderate and severe' is vague in reference to the definition of mild moderate to severe and should be clarified to include reference to signs and symptoms assessment tools. Additional context similar to what is discussed in section 7.2.2.1.2 is recommended. Proposed change: It is recommended to use a stratified randomisation according to disease activity (e.g. mild, moderate and severe) as judged by mucosal inflammation (e.g. ~~mild, moderate and severe~~ CDEIS or SES-CD) and/or signs and symptoms (e.g. CDAI or a qualified PRO tool).	Partly accepted. Clearer guidance on the definitions of mild-moderate versus severe has been provided. However, it is the intention to base this stratification on as objective findings as possible (endoscopic appearance) and not to let it be driven by subjective symptoms that varies greatly from patient to patient.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
221-222	4	Comment: The draft guidance recommends using a stratified randomisation according to disease activity as judged by mucosal inflammation e.g. mild, moderate, and severe. We believe that this advice is premature given that the assessment of mucosal inflammation in clinical trials in CD is a relatively new concept with data only now being generated to evaluate, validate, and replicate clinically meaningful thresholds if applying the SES-CD or CDEIS endoscopic assessments with even more limited data for MRE.	Not accepted. Please see response to previous comment.
225-226	4	Comment: The sentence beginning with ”mode of delivery” is unclear in the setting of a paragraph discussing randomization strata and subgroup analyses.	Accepted
234-236	4	Comment: For biologics that do not normally involve CYP enzymes in their metabolism processes, could interaction studies be waived if MOA of the drug indicates no mechanism to cause interaction?	Not accepted. This is a general issue for interaction studies and is dealt with in other existing guidelines. No changes necessary.
234-236	4	Comment: The recommendation to study the efficacy and safety implications of concomitant drugs likely to be co-administered in clinical practice appears to contradict lines 200-201.	Partly accepted. The issue of concomitant steroid treatment has been clarified. The recommendation in this section is still valid and does not contradict previous recommendations.
253-255	4	Comment: It is unclear what, in the sentence regarding escape procedures, is meant by “should secure a meaningful comparison of the treatments.” Sponsors cannot know a priori how many patients will drop from each arm of a study, and cannot force subjects to remain in a study and receive the pre-specified period of follow up; clearer guidance on what is expected here is needed.	Accepted. Sentence has been deleted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
272 and 283	4	Comment: Endoscopic entry criteria will select a different trial population than in real world, where endoscopy is unlikely to be repeated before each treatment change/initiation; thus it needs to be recognized that this may cause discrepancies between clinical trial and real world treatment outcomes;	Not accepted. It is acknowledged that the proposed strategy differs from the previously recommended regulatory guidance and that to some extent it also differs from clinical practice, at least in some instances. However, there is increasing evidence that in in case of symptomatic relapse, evaluation of objective signs of inflammation is mandatory to avoid treating non-inflammatory causes of symptoms with drugs that target the inflammatory process (and thus have a low likelihood of being successful against non-inflammatory causes). Thus, the differences between clinical trial and real world outcomes is likely to be small.
277-278	4	Comment: We think that both steroid dependent and refractory subjects should be able to enter study receiving concomitant corticosteroid up to a set maximum dose. We also recommend that patients continue to receive concomitant medications including corticosteroids at the start of a clinical trial. Patients who meet eligibility criteria in the setting of stable concomitant medications have sufficiently severe disease activity to warrant inclusion in clinical trials. Proposed change: Delete statement: ~~"Except for steroid-dependent patients, patients should preferably be off steroid when entering studies".~~	Accepted.
278-279	4	Comment: We agree with the recommendation (lines 124-125) that "Tapering schedules must be standardized and too rapid tapering avoided", but we do not agree with the recommendation to taper corticosteroids during the induction period.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The reasons to maintain stable corticosteroid doses during the induction period include the following: There would be insufficient time to taper corticosteroids prior to the primary endpoint assessment using the type of tapering schedule generally applied in CD clinical trials. A rapid corticosteroid taper prior to the primary endpoint assessment may precipitate clinical flares that would impact patient well-being and could present challenges to the interpretation of the treatment effect during the induction period. Specifically, a rapid taper of corticosteroids during the induction period could confound the assessment of efficacy in the setting of additional medication changes. Furthermore, a rapid steroid taper may introduce an imbalance in efficacy in the Placebo vs active treatment group that could result in lower efficacy in the PBO group and would confound assessment of efficacy. Withdrawal of corticosteroids prior to the induction primary endpoint could also lower the number of patients that may be ultimately eligible for the maintenance study. In our CD clinical trials, corticosteroid tapering is mandatory in clinical responders using defined criteria over a longer time period during the maintenance period.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Subgroup analyses of induction and maintenance CD 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 maintenance steroid tapering to demonstrate the benefit of the active study treatment vs. Placebo for achieving and maintaining clinical remission. Proposed change: Delete reference to steroid taper during induction.	
280-282	4	Comment: As there are currently no fully validated PROs inclusion criteria based on signs and symptoms may use the CDAI score (e.g. at least 220) or the "PRO2" (e.g. of at least 14) until a validated scale is available, but patients included must also have a certain minimal level of mucosal inflammation (e.g. a score >8 when using CDEIS or a score >6 when using SES-CD). Please include reference to PRO3 and a score in this area of guidance as both have been considered equally valid in retrospective analysis of clinical trial outcomes. Proposed Change: As there are currently no fully validated PROs inclusion criteria based on signs and symptoms may use the CDAI score (e.g. at least 220) or alternatively the "PRO2" (e.g. of at least 14) or the	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"PRO3" (e.g. of at least 22) until a validated scale is available..... (as per the reference Khanna R, Zou G, D'Haens G, Feagan BG, Sandborn WJ, Vandervoort MK, Rolleri RL, Bortey E, Paterson C, Forbes WP, Levesque BG. Aliment Pharmacol Ther. 2015 Jan;41(1):77-86)	
281	4	Comment: Please clarify how PRO2 is calculated in the example using a value of 14. Is this an average daily value of the weighted sum of the SF and AP components?	Not accepted. This is clearly described in the reference cited by the stakeholder. It is not necessary to include this in the guideline
301 – 302	4	Comment: The guidance for second line indication asks that the established therapy is continued as background therapy in the control arm. A common reason for failing the established therapy is intolerance (subjectively or objectively) and/or safety findings leading to treatment discontinuation. It is not possible to continue the existing treatment in these cases. Similarly, patients may fail a TNFα inhibitor due to the development of neutralizing antibodies. As these patients would have no benefit from continued treatment, but possible risks, it might also not be advisable to continue this therapy as background therapy in the control arm. We would appreciate increased detail in the guidance clarifying in which cases the background therapy may be discontinued at study start. Proposed change (if any): For a second-line indication in patients with insufficient response to established therapy, it is advised that the established therapy is	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		continued in the control arm as background therapy (if no intolerance to the established therapy and if some residual benefit is reasonably possible). While in the experimental arm, established therapy (add-on) or placebo may be used in combination with the experimental agent	
307-308	4	Comment: The guidance states that for patients with severe, steroid and immunosuppressive refractory CD, a comparison with an anti-TNF compound is recommended. Current CD programs are broader and enrol moderate to severe CD patients. We do not support the enrolment of a more restricted patient population. Further, these patients (be they moderate or severe) are more likely to have received biologic therapy, including one or more anti–TNF to which they may have demonstrated refractoriness. This latter point complicates the selection of an appropriate active comparator. In regard to the recommendations favouring separate induction and maintenance studies and comparator recommendations in section 7.2.2.2.2, 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	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		through methodology.	
313	4	Comment: “Patients who are presently on the test drug should be randomised to continuing the test drug or switching to …” It seems clear from the chapter 7.2.2.2.2 below that re-randomisation is what is meant in this sentence Proposed change (if any): Patients who are presently on the test drug should be **re-**randomised to continuing the test drug or switching to …	This section has been revised
320	4	Comment: We request clarification that "The treatment period should be aimed at a minimum of 12 months", means a combination of exposure that includes both induction and maintenance therapy (i.e. a total of 12 months).	Accepted
322-324	4	Comment: The guidance states that "Patients who are in remission (as defined above) and off steroids may be included into maintenance trials". As indicated in the response to lines 278-279 of the guidance above, we have concern regarding the tapering of steroids during a 6-8 week induction study and therefore, this concern carries over to the definition of the target population for maintenance studies. We continue to 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	Partly accepted. Point 1 and 2 are accepted whereas point 3 is not. Please refer to previous responses.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		secondary analyses for maintenance of clinical remission and steroid-free remission with appropriate statistical controls. Please also see additional comments regarding treat-through design in two other sections. Proposed changes: 1) Acknowledge that patients in clinical response are an appropriate primary target population for the assessment of maintenance therapy. 2) 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. 3) Consider the evaluation of maintenance efficacy at the population level (i.e. the entire randomized population from induction, rather than just induction responders/remitters).	
323-324	4	Comment: The requirement that patients who enter in maintenance trials be (1) off steroids, (2) in complete MH (SES-CD of 0), and (3) in clinical remission, will result in a situation that requires thousands of patients to be entered into induction trials in order to identify adequate patients for maintenance trials. It is not reasonable to expect large numbers of patients can achieve this highly stringent endpoint within 12 weeks. Consideration to the appropriate selection of patients into a maintenance trial should also be given to the patient population under study and the unmet medical need.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
	4	Comment: In addition, the requirement contradicts the concept of co-primary endpoints for MH and clinical remission as opposed to the secondary endpoint of 'Individual patients achieving both MH and symptomatic remission' (line 204).	Accepted
328-332	4	Comment: This section is inconsistent with the paragraph in lines 322-327.	Accepted
328-341	4	Comment: Also refer to comments in response to Lines 148-153. The notion that true maintenance of efficacy can only be demonstrated in the context of a randomized-withdrawal study (vs. placebo) or only among induction responders/remitters is concerning. As discussed in an earlier section, the arbitrary designation of induction and maintenance study periods limits one's ability to evaluate the true efficacy potential of a MOA; and is highly inconsistent vs. clinical practice. The maintenance of efficacy among "induction responders" only provides insights into the continued benefit observed among patients who achieved an initial response/remission within an arbitrarily set "early" timeframe, but ignores the rest of the population treated. Whereas, the holistic approach under a treat-through study design, will support the evaluation of long-term efficacy at a population level, including both early and late responders to initial (induction) treatment and their response to continued	Partly accepted. The section has been rewritten to allow inclusion of responders into the maintenance phase and to allow a treat through design. However, the randomised withdrawal study design is also recommended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		long-term treatment (maintenance), and will also support the desired “maintenance of remission among induction remitters” analysis. In addition, evaluation of endoscopic/ histologic endpoints would be significantly challenged in the setting of a randomized-withdrawal (to placebo) study, since the kinetics of disease worsening (upon discontinuation of treatment) by these outcomes measures are unknown. A treat-through study design is much more favourable and preferred for the evaluation of these important outcomes. It should be noted that comparison to standard of care comparators (e.g. anti-TNF) using this methodology incurs substantial complexity. We believe comparison to SOC in both induction and in maintenance phases of treatment as part of the confirmation study is best accomplished using a treat through methodology. Finally, the validity or requirement of a randomized withdrawal (to placebo) design to demonstrate the need for maintenance treatment in patients with CD should be questioned. After 20 years and numerous trials across different MOAs, there is no evidence that patients with CD 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	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		withdrawal placebo studies are inconsistent with clinical practice and is a design feature that is a significant deterrent to patient recruitment.	
343	4	Comment: 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. This may affect the availability of new and potentially effective medications for Crohn's disease in the European Union. Proposed change (if any): The recommended endpoint should be changed to the proportion of subjects in clinical response at the end of the maintenance period.	Partly accepted. It is accepted that evaluation of efficacy should be done at the end of the maintenance phase. The two co-primary endpoints (1. clinical remission of steroids and without surgery and 2. Endoscopic remission) is maintained as it is considered important that future drugs for the treatment of CD demonstrates efficacy in both of these aspects.
356-361	4	Comment: see response to lines 307-308 and 328-341 of the guidance. Further, expectations of superiority and non-inferiority should be further elaborated. There are no controlled studies available using the new endpoints in the evaluation of standard of care products. Therefore it is has not been established that even standard of care products would meet the newly proposed and non-validated endpoints proposed. This makes the implementation of active comparator studies using these new endpoints unaccompanied by the traditionally applied CDAI difficult to appropriately	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		plan (e.g. power). It should be noted that comparison to standard of care comparators (e.g. anti-TNF) may be best accomplished using a treat through methodology.	
357-361	4	Comment: Please clarify how a comparator trial is possible in a "maintenance setting." It does not seem appropriate to compare outcomes in a group of patients all induced with one agent to be maintained on different agents.	Partly accepted. It is stated that active comparator is more easily implemented in treat through studies.
361	4	Comment: As randomized withdrawal studies will be standard design in maintenance trials, it is unclear how a TNF comparator should be included in a PBO controlled trial; should patients responding to the IMP be switched to anti-TNF? This will for such patients double the number of treatment groups with increased risk to fail: PBO and anti-TNF. Ethically a dilemma and not representing real-word practice, as responders to one drug would not be switched to a different drug.	Accepted
381-382	4	Comment: EMA should clarify if "*at least 12 weeks of follow-up without treatment*" is needed as already demonstrated in maintenance treatment (placebo arm).	Accepted. This sentence has been deleted
400-401	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." 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**	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		provided post marketing Proposed change (if any): Furthermore, it is important to get information on re-treatment outcomes even after a longer time interval without treatment with a specific drug, this should be considered as part of post marketing commitment	
404-422	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. I 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 paediatric subjects with rare, monogenic causes for IBD, in pediatric clinical trials that are designed to investigate idiopathic IBD. Proposed change (if any): 1) Consider rewording this section to base the pediatric subject's age on the age at diagnosis, rather	Not accepted, we agree that VEOIBD is defined as IBD onset <6 years, but not every IBD is monogenic at that age and treatment could be same. We stated before: "Younger children should be genetically tested for known immunological defects and in- or excluded depending on the defect". The sentence has been adapted for clarity.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		than the current age of the subject. 2) Consider explicitly using the term “Very Early Onset IBD” to make it clear that the intention of this guidance is not to mandate the inclusion of pediatric subjects with rare, monogenic causes of IBD in trials designed to include subjects with idiopathic IBD. The Agency should consider communicating a clear expectation that rare, monogenic causes of IBD will be considered orphan diseases.	
409	4	Comment: Please clarify that paediatric Crohn’s disease is a rare disease in younger children. Proposed change: **Paediatric** CD is **a** rare **disease** ~~in children below 10 years of age~~ and younger children **(i.e. under 4 years of age)** may develop a different disease phenotype compared with adolescents or adults.	Accepted
411	4	Comment: Please consider increasing the minimum age for children to be studied to 7, since, as pointed out on lines 409-410, young kids may have a different disease phenotype.	Not accepted. Sentence in text adapted.
414-415	4	Comment: Please clarify the term “younger children” by adding an age. We agree to genetically testing children, but should not be the sponsor´s burden. Proposed change: “Younger children **<6 years of age** should ~~be~~ **have been** genetically tested for known immunological defects and in-or excluded depending on the defect”	Accepted. Children at younger ages are genetically tested, inclusion is also a responsibility of the physician.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
421-422	4	Comment: Proposed change: "EEN treatment ~~should~~ **may** be considered as a comparator in **unblinded** trials designed for the products for first-line therapy".	Partly accepted, we cannot blind EEN trial
434-435	4	Comment: There are cases that could apply for a "partial extrapolation plan", in which a small E-R study being done to demonstrate similarity of E-R relationship between adults and children and subsequently allowing extrapolation of adult's data. Proposed change (if any): We suggest adding a "partial extrapolation option" in this guideline.	Not accepted, is only a wording
437	4	Comment: Proposed change: • Whether the substance belongs to a well-studied pharmacological class for which several substances have already been granted a paediatric indication, **or have already established exposure-response relationship in both children and adults**	Accepted
446-466	**4**	Comment: It would be helpful to have more guideline on dose finding study in the paediatric population.	Not sure what they expect…
461-466	4	Comment: Please clarify what prospective data support Trough or AUC-based dosing in any population, given that "therapeutic" thresholds have not been established for the majority of drugs in use for CD in children or adults. Please clarify what labelling would be allowed based on this kind of study. Please keep in	With respect to what is written in section 8.3.1.1 Extrapolation exposure reflected by AUC or Ctrough measured in a primary population where the IMP proved effective may be used as a basis for dose selection in a pediatric study, text has been adapted for clarity.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		mind to perform this type of study requires significant logistical challenges in order to maintain blinding.	
469	4	Comment: The definition of remission here appears to be a composite, not co-primary endpoint, in contradiction to what is recommended for adult studies. Please clarify.	Partly accepted, changed as follow: Remission should be defined as clinical remission and endoscopic MH, as co-primary endpoints.
469	4	Comment: Please clarify whether the clinical remission definition is the same for both adults and children.	Clinical remission for both adults and children, is defined as absence of signs and symptoms.
470-471	4	Comment: Please be aware that the requirement to perform endoscopy 3 times during an induction/maintenance study (BL, induction endpoint, and maintenance endpoint) is not well accepted by investigators, parents, or patients, and limits what is already very challenging enrolment in a rare disease state with a high unmet need. Please consider the contribution of this expectation on the already lengthy delay after adult approval in bringing drugs to market for pediatric IBD. Given that this document requires established efficacy and safety in adults for extrapolation (line 431), the pediatric studies cannot start until the adult studies are completed and analysed.	Not accepted, in clinical practice we do not need many of endoscopies, but for drug development and MH as endpoint we need to keep 3 endoscopies.
470-474	**4**	Comment: Although endpoints based on assessment of the intestinal mucosa are currently under development in adult Crohn's disease populations, these are not currently suitable for use as primary endpoints in children for the following reasons. 1. Even in adult populations, mucosal healing has not been used as the primary endpoint in any Phase 3 study in Crohn's disease. As such mucosal healing	Not accepted, mucosal healing should be the primary endpoint, repeated endoscopies does not represent higher risk than uneffective treatment. Especially in drug with new mechanism of action, pediatric population is vulnerable and benefit must be clear.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		should not be a primary endpoint in paediatric Crohn's disease studies unless it is the primary endpoint in the supporting adult studies, as the use of divergent endpoints would prevent extrapolation of efficacy from adult to children. While newer adult studies often do study mucosal healing, provisions should be considered for such products in which insufficient data are available on this endpoint in adults. 2. While the use of mucosal healing as a primary endpoint is conceptually appealing, there is a lack of clarity regarding definitions of mucosal healing. For example, some studies have defined mucosal healing as the absence of any ulceration, while others have utilized one of a number of scoring systems. There is also a lack of consensus on the use of histologic data in the assessment of mucosal healing. Until these operational criteria are defined in adult populations and are agreed upon by the health authorities for standardized use in adults trials, and a harmonized position is reached between major regional health authorities, it would premature to require these endpoints in children. 3. The validity of mucosal healing as a predictor of long-term outcome in adults or children has not been established (i.e. prospective treat to target studies (to achieve mucosal healing) and the	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		association with long-term hospitalization, rate of surgery, etc.). Endoscopic assessments are inherently limited by their inability to assess sub-mucosal disease or the mucosa of the mid-small bowel. 4. A requirement for endoscopic assessment of mucosal healing poses additional risk to paediatric subjects. "Although serious risks such as perforation, bleeding or anaesthesia complications are low (Hsu et al 2013), colonoscopy is often accompanied by risks from the bowel prep, including abdominal pain, diarrhoea, vomiting, and dehydration." 5. Any procedure posing more than minimal risk to vulnerable populations such as children must be associated with a clear benefit, which is not currently the case. Please note that approximately 35% of colonoscopies in children with IBD fail to intubate the terminal ileum. Therefore, the main site of disease in children is often not visualized during endoscopic evaluation limiting the utility of endoscopy as a primary endpoint (Batres et al 2002). 6. If the primary endpoint of a paediatric study is mucosal healing, the study would likely have to exclude subjects without mucosal ulcerations at baseline. Such a study would not be assessing the efficacy of the product in improving symptoms in all pediatric patients with CD, including those without mucosal involvement. For example, in a	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		study of infliximab in adults with CD, approximately 70% of the subjects had mucosal ulcerations at baseline, while approximately 30% did not have mucosal ulcerations (Colombel et al, 2010). 7. A requirement for endoscopic assessment of mucosal healing is likely to delay approval of new drugs for Crohn's disease in children because it poses an additional barrier to the feasibility of recruitment of studies in children with CD. Parents/caregivers are less likely to provide consent for participation in studies requiring endoscopy/colonoscopy,. Studies with colonoscopies are more difficult to enrol than studies without colonoscopies. This issue, in combination with the fact that approximately 30% of the otherwise eligible subjects with CD will not have mucosal ulcerations at baseline (see previous point), could result in the need for a substantially longer enrolment period and delayed access to the product. 8. It is anticipated that there may be challenges interpreting results based on a primary endpoint that depends on repeat colonoscopies. Specifically, a high dropout rate is often seen in studies requiring follow-up colonoscopies. In a study with infliximab in adults with CD, between one-third and one-half of subjects did not have a follow-up colonoscopy at Week 26 (Remicade EPAR). A	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		higher dropout rate would be expected in a pediatric study due to the inconvenience and hardship for children and their caregivers. Moreover, the pattern of dropout may skew results. For example, it is expected that non-responding subjects who may be considering study discontinuation may have a higher dropout rate than responders. Notwithstanding the above points, the company does acknowledge that there may be a role for endoscopy/colonoscopy to confirm mucosal healing in subjects in long-term remission. **References:** Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010;362(15):1383-1395. Batres LA, Maller ES, Ruchelli E, Mahboubi S, Baldassano RN. Terminal ileum intubation in pediatric colonoscopy and diagnostic value of conventional small bowel contrast radiography in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2002 Sep;35(3):320-3. Hsu EK, Chugh P, Kronman MP, Markowitz JE, Piccoli DA, Mamula P. Incidence of perforation in pediatric GI endoscopy and colonoscopy: an 11-year experience. Gastrointest Endosc. 2013 Jun;77(6):960-6. doi: 10.1016/j.gie.2012.12.020. Epub 2013 Feb 20.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Remicade EPAR EMEA/H/C/000240/II/00142, Table 8 (http://www.ema.europa.eu)	
471	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.
472-473	4	Comment: This sentence contradicts the sentence on line 469.	Not accepted
472-473	4	Comment: Please clarify that clinical remission and endoscopic MH could be separated in time. How to re-randomise, based on the co-primary endpoint? Can you re-randomise based on response?	Clinical remission should be followed by MH, rerandomisation cannot be based on response only.
472-474	4	Comment: the agency recommends a Paediatric patient reported outcomes (pPRO) as co-primary endpoint (instead of activity scores) as soon as a validated tool is available". Also the Agency proposes inclusion of children from 2 years of age in pediatric studies, but patients are not able to reliably self-report before age 8 (see Matza et al; https://www.ispor.org/workpaper/PROchildrenadolescents/Matza_et_al_2013_ISPOR_Task_Force_PROs_in_Children.pdf) and reliability of responses after that age will be determined by cognitive development. It is recommended that the agency indicate preference among (a) a measure of signs, to be measured by the HCP (ClinRO)/parent (ObsRO) in all paediatric patients only, (b) signs and symptoms reported by the patient (PRO) when they are "able" to do so, with no measurement in younger patients, or (c) some combination thereof?	pPRO should be used in relevant population, in younger children we need to use other measures
475	4	Comment: Please clarify how PCDAI is defined in	Nowadays is PCDAI widely used, definition is clear and should

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		clinical remission.	be associated with other parameters (MH, pPRO,…)
475-478	4	Comment: Until properly developed and validated patient-reported outcome measures of Crohn's disease symptoms are developed, new studies for drug approval in children should use prior standard measures (e.g. PCDAI). Endpoints that reflect the patient's report of his or her symptoms of Crohn's disease) should be a central component of drug development for children with Crohn's disease. These endpoints should be defined using formally developed and validated patient-reported outcome measures. Currently, there are no such measurement tools available for adults or children with CD; these are currently being developed.. In the interim, existing validated measures that include symptom-based components (e.g., the PCDAI) should be used. Proposed change: Acknowledge that until properly developed and validated patient-reported outcome measures of Crohn's disease symptoms are developed, new studies for drug approval in children should use prior standard measures (e.g., PCDAI).	Accepted
493-496	4	We appreciate the recognition regarding the difficulty of the use of placebo in pediatric CD studies. We would like to point out that NI studies are likely to be extremely large (hundreds of patients) and executing this type of trial is infeasible, especially if endoscopic examinations are required.	The right choice of development strategy depends on multiple factors such us availability of adult data, class of products and other pediatric indications data.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
498-499	4	Comment: Please clarify what is the “risk of lack of efficacy”. Proposed change: “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
503-507	4	Comment: Please provide further guidance on how to re-randomise with an active comparator.	Re-randomisation refers to the placebo control trial.
515	4	Comment: Please specify “development”. We propose to change the wording to “growth velocity” Proposed change: **“…** are necessary to determine possible effects on maturation and ~~development~~ **growth velocity**”.	Accepted,
519-521	4	Comment: Not all new mechanisms of action for the treatment of CD may impact adaptive immunity. If preclinical data exist demonstrating that vaccination responses are not affected, this should suffice. We suggest removing 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 or where preclinical data suggest increased risk of failed vaccination.	Not accepted. Animal data are not predictive of clinical vaccination data. Innate and adaptive immunity are one these days. Response to vaccination should be assessed in no inferiority design to age related vaccination strategies in European countries. Follow up of serum antibody response over time is necessary.
525-527	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	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
525-527	4	Comment: Cooperation with other global regulatory agencies is appreciated as it relates to mandates regarding post-marketing registries. Support in establishing disease-based registries that can be used to achieve these goals would be much appreciated as this is unlikely to be able to be accomplished by sponsors alone.	Accepted
101	4	Comment: "The majority of patients experiences"	Not accepted. (the majority (of patients) experiences)
	4	Comment: The formatting of the guidance regarding the use of a comparator is not entirely consistent within the document. For example, the comparator is described in the appropriately labelled comparator sections and also in the section on study design.	Partly accepted. It has proven difficult to keep the separation throughout the document. The document has been revised to provide better separation, albeit not perfect.
103-106	4	Comment: Proposed change: "…demonstrating efficacy in this situation should have evidence of active mucosal inflammation documented by recent endoscopy (ileocolonic disease) and/or imaging of the ~~small intestine~~ **gastrointestinal tract** (e.g. magnetic resonance enterography (MRE)/capsule endoscopy) (~~small intestinal disease only~~)".	Not accepted. In ileocolic disease, the preferred way of documenting inflammation is endoscopy. From a diagnostic point of view, endoscopy (enteroscopy) is also the preferred method for documenting inflammation in the small intestine. However, enteroscopy is a demanding procedure for both patients and doctors. Thus, in this instance MRE/capsule endoscopy may be used for documentation of inflammation at inclusion, inspite of the lack of formal validation.
139-141	4	Comment: Proposed change: Consider moving the following sentence to background section in the guideline: "Remission can be achieved either by medical treatment or surgery".	Accepted
150	4	Comment: further define "treat-through" upfront, definition is only given later line 334	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): include here the definition provided line 339	
174-175	4	Comment: Proposed change**:** Symptomatic relief should be evaluated by patient ~~related~~ **reported** outcomes (PRO) (e.g. number of lo**o**se stools and abdominal pain).	Partly accepted. Reference is made to the subsequent section where this design is defined.
345	4	Comment: "Time to event analysis is only consideres supportive as just pronlonging time to relapse without decreasing the end of study risk is not considered a relevant benefit" Correct typos and precise what "end of study" mean in this context Proposed change (if any): Time to event analysis is only considered supportive as just prolonging time to relapse without decreasing the end of study risk is not considered a relevant benefit	Accepted
106	5	Comment: Why is the EMA limiting MRE to small bowel only? Proposed change (if any): Suggest being able to detect evidence of mucosal inflammation via MRE for the entire bowel	Not accepted. Please refer to previous response regarding lack of validation of MRE.
137-138	5	Comment: The definition of mucosal healing is not standardized across agencies in different regions. FDA specifically stated that mucosal healing should not be defined by macroscopic signs of inflammation by	Partly accepted. In the literature, mucosal healing is most often defined as absence of macroscopic (endoscopic) signs of inflammation. Nevertheless, it has been clearly defined that in this guideline mucosal healing is defined as endoscopic

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		endoscopy, and rather by histology. Given phase three studies in Crohn's disease as by necessity global studies, differing definitions will lead to confusion and potentially badly designed studies. Proposed change (if any): Suggest either using a globally accepted standard definition of mucosal healing globally, or call it endoscopic remission instead.	healing.
158-159	5	Comment: "Ultimate treatment goal …. is steroid free clinical and endoscopic remission." is limiting to patients that can be assessed by endoscopy Proposed change (if any): Clarify statement to include other imaging modalities, where applicable	Partly accepted. However, at present there are no fully validated instruments for determining drug effect on more proximal small bowel.
181-185	5	Comment: No advice on the use of MRE endpoints is provided to evaluate mucosal inflammation	Accepted
188-189 200-202 277-279 343-345	5	Comment: Much emphasis has been placed on application of steroid free remission as 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 It is advised that induction should be at least 8 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	Accepted. This part of the guideline has been revised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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. In addition, recommendations for steroid sparing as a primary endpoint is not consistent with recent national agency advice for phase 3 designs. Consistent with the draft guideline's Methods to Assess Efficacy Criteria, the use of patient related outcomes and endoscopy were recommended by member state agencies, but not in the context of steroid free remission. Proposed change (if any): Provide more clarity on how steroid sparing can be calculated and used in any supporting claim	
188-189 200-202 277-279 343-345	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 MAA, 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.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Provide clear, expected study designs for registration.	
221-222	5	Comment: The guideline recommends using disease activity as judged by mucosal inflammation, e.g. mild, moderate and severe. Proposed change (if any): Provide clarity on the definition of “mucosal inflammation” – whether it means endoscopic or histologic as it is used interchangeable throughout the document. Also, define what constitute mild, moderate and severe mucosal inflammation.	Accepted. Clarification has been provided.
278-279	5	Comment: For steroid dependent subjects, the guideline recommends that it should be tapered before evaluation of efficacy. This will introduce a significant confounding variable in the induction study. Proposed change (if any): Provide clarity on this approach and rationale for it.	Accepted
322-324	5	Comment: Requiring patients to achieve both clinical remission and endoscopic remission (SES-CD or CDAIS of 0) within 12 weeks off steroids before entry into the maintenance study is an extremely ‘high bar’ for efficacy.	Accepted
352-353	5	Comments: Patients who leave the study with treatment outside the protocol are recommended to undergo the full period of planned follow-up. However, introduction of any treatment other than study drug will confound safety signal and increase study	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		procedure related adverse events (e.g. blood draws, possible endoscopy etc.). Also, patients withdraw consent when they leave the study and the sponsor cannot require them to continue to follow up in the study according to the good clinical practice guidelines.	
Additional comment	6	General comment: Proposed added text is underlined, proposed text to be removed is ~~striked through~~.	Not accepted. The WORD track changes function is used.
1-533	6	Comment: Recommendations in proposed guideline should be specified more clearly to avoid misinterpretation as much as possible.	Accepted
78-85	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 scientific guideline on Crohn's disease.	Not accepted. This hold true for all guidelines and is not specific for this one.
129-131	6	Comment: Active disease despite prednisolone dosing up to 0.75 mg/kg/day over a period of 4 weeks concerns steroid-refractory disease according to current ECCO guideline on definitions and diagnosis of Crohn's disease (Van Assche et al. 2010). This should be indicated. Proposed change (if any): *For example according to the ECCO guideline, patients who have active* Crohn's *disease despite prednisolone of up to 0.75 mg/kg/day over a period of 4 weeks* are considered refractory to steroids.	Accepted
144	6	Comment: An editorial change is proposed. Proposed change (if any): *… should be demonstrated.*~~;~~	Accepted
151-152	6	Comment: Effects of study treatment with respect to	Not accepted. The treat through design mimics clinical practice

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		induction of remission and maintenance of remission should be evaluated in separate studies (see General comments above). Hence, 'threat through' design is not recommended. Proposed change (if any): 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	and is similar to what is being used for other inflammatory conditions such as rheumatoid arthritis.
155	6	Comment: An editorial change is proposed. Proposed change (if any): *… adequately demonstrated*.~~.~~	Accepted
187-195	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). A sentence about steroid tapering is stated twice in the primary endpoint section. One of these sentences should be removed. Proposed change (if any): **Co-p~~P~~rimary endpoints** Treatment of Crohn's disease is aimed at inducing and maintaining both symptomatic and endoscopic	Partly accepted. The comment is generally acceptable. The section has been revised. However, the exact wording has been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		remission, if possible without concomitant steroid treatment. Because of this, co-primary endpoints of both induction and maintenance treatment should concern: (1) the proportion of patients with symptomatic, and (2) the proportion of patients with endoscopic remission. Important secondary endpoints concern the proportions of patients in whom either or both of these co-primary endpoints are met without steroid treatment (see below). Further, the change in use of corticosteroids – especially in the maintenance phase – is of interest. ~~Achieving/maintaining symptomatic remission free of steroids is an appropriate primary endpoint. In patients receiving systemic steroids, these should be tapered according to predefined schedules.~~ *Remission should be defined and justified according to the instrument used for evaluating.* ~~E.g., when evaluated by a 5-point scale,~~ S*symptomatic remission can be defined as "no" or "mild" symptoms.* ~~However as previously noted, achieving/maintaining MH should also be considered a primary endpoint. As for the symptomatic endpoint, remission should be defined and justified according to the instrument used for evaluating. E.g. when evaluated by~~ Endoscopic remission, i.e. mucosal healing (MH), may be defined	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		as a Crohn's Disease Endoscopic Index of Severity (*CDEIS*)~~, a~~ *score of 0* ~~can be used for defining remission in terms of mucosal inflammation~~. *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 two co-primary endpoints depends on the aim of the treatment (please see below) as well as the pharmacodynamic properties of the test drug.* *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.*	
203	6	Comment: Ultimate treatment goal of Crohn's disease treatment concerns induction and subsequently maintenance of remission 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,	Not accepted. In order to allow inclusion of patients on corticosteroids and in order to avoid the confounding effect of tapering of steroids in short term studies, the guideline has been revised to allow stable doses of steroids in the induction phase. However, for the maintenance phase steroid free remission is maintained as the primary endpoint and steroids should be tapered in the early part of the maintenance phase.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		it is recommended that doses of steroid treatment at which remission is obtained are reported. Respective secondary endpoints should be evaluated in clinical studies. Proposed change (if any): The following text should be inserted at the start of the secondary endpoint section: Treatment of Crohn's disease 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: - proportions of patients in whom either or both symptomatic and endoscopic remission are achieved without concomitant steroid treatment. - 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). These endpoints should be evaluated in all clinical studies in which concomitant steroid treatment is allowed. Other recommended secondary endpoints concern: 1. *Individual patients achieving both MH and symptomatic remission* 2. (…)	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
205-206	6	Comment: Proposed secondary endpoint 'Remission defined slightly differently from the primary endpoint (e.g. use the more stringent approach, if a less stringent approach has been chosen for the primary endpoint or vice-versa)' is unclear. As it is unclear what is meant, its relevance to clinical practice is also questioned. Proposed change (if any): It is proposed to remove secondary endpoint mentioned above.	Partly accepted. This endpoint has been included to allow a better description of the efficacy of the drug in terms of providing macroscopic healing of the mucosa. It is agreed that the wording is not precise. The guideline has been revised provide a clearer description (please see previous comments).
219	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 203, it is recommended to adjust proposed secondary endpoint on steroid sparing effects. 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.	Not accepted. Please see above.
280-283	6	Comment: Proposed inclusion criterion with respect to patient-reported outcomes is unclear and therefore needs some more specification. Particular CDAI subscores may be helpful. Motivation: In revised guideline, it is proposed to include study	Partly accepted. The PRO2 is derived from the CDAI subscores (Aliment Pharmacol Ther 2015; 41: 77–86). This has been stated and reference has been made to this publication.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		patients based on both CDAI scoring, or 'PRO2' until a validated patient-reported outcome scale is available AND based on level of mucosal inflammation. The term 'PRO2' is vague and therefore needs to be specified. It is assumed that CDAI subscores with respect to 'number of liquid or very soft stools' and 'abdominal pain' are meant. In several recent central scientific advices with respect to Crohn's disease (i.e. risankizumab, ozanimod), particular CDAI subscores, i.e. stool frequency score of ≥4 or an abdominal pain score ≥2, were accepted as part of the inclusion criteria for clinical studies on moderate to severe Crohn's disease. In the ustekinumab scientific advice (EMA/CHMP/SAWP/ 474703/2016), it was recommended to use total CDAI scores in order to 'cross validate' inclusion criteria based on CDAI subscores with respect to stool frequency and abdominal pain. Hence, (combinations of) CDAI subscores may be used in addition to the total CDAI score. This should be stated in revised EMA guideline on Crohn's disease. Proposed change (if any): *As there are currently no fully validated* patient reported outcomes (*PROs*) *inclusion criteria based on signs and symptoms may use* total *CDAI score*s *(e.g. at least 220)* ~~or~~with or without ~~the "PRO2"~~ (combinations of) CDAI subscores (e.g. ~~of at least 14~~ a stool frequency score ≥4 OR abdominal pain score ≥2 in case of mild to moderate disease) *until a validated scale is available, but*	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		patients included must also have a certain level of mucosal inflammation (e.g. a score >8 when using CDEIS or a score >6 when using SES-CD).	
328-337	6	Comment: See general comment above with respect to induction and maintenance treatment. Proposed change (if any): It is proposed to remove lines 328-337 (Trials combining … 'maintenance of efficacy'.).	Not accepted. All recently developed drugs for treatment Crohn's disease has been intended for long term treatment making the distinction between induction and maintenance artificial. The guideline should include recommendation for this modern approach to treatment.
402	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). 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. Proposed change (if any): Elderly patients 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.	Accepted

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403-444	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. Motivation: In lines 410-414 the importance of including paediatric patients from 2 years and above with Crohn's disease in clinical studies is discussed. By contrast, in lines 424-425 it is stated that based on similarity of Crohn's disease 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 Crohn's disease studies should be carefully assessed. Proposed change (if any): For clarity and to avoid misunderstanding, the discussion on the need for paediatric studies should be integrated.	Not accepted, the statement is clear and not contradictory.
404-408	6	Comment: Paediatric patients with Crohn's disease are at increased risk of impaired growth and sexual maturation (Malmborg & Hildebrand 2016), and also reduced peak bone mass (Bailey 1997). This is caused by factors such as undernourishment and pro-inflammatory cytokines (Shamir et al. 2007; Kirschner et al. 1981). A statement about this should be included in revised EMA guideline. Proposed change (if any): *CD is similar in adult and paediatric patients in terms of overall disease*	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		pathology and progression and possible treatment targets. However, paediatric forms of IBD are characterized by a more complicated disease course with higher inflammatory activity and higher need for corticosteroids and immunosuppressive therapy. Subsequently children have a higher cancer risk, longer duration of disease, severity or extension of disease compared with adult-onset IBD. In addition, paediatric patients with Crohn's disease are at increased risk of growth failure, retarded puberty, and reduced peak bone mass due to factors such as undernourishment, and pro-inflammatory cytokines.	
467-481	6	Comment: Like in adult patients, co-primary endpoints of pharmacological treatment of paediatric patients with Crohn's disease should concern the proportion of patients in symptomatic remission, and endoscopic remission (i.e. mucosal healing) respectively. As growth, maturation, and bone mass may be impaired in paediatric Crohn's disease 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. Proposed change (if any): ***8.3.1.3. Efficacy in paediatric patients*** *Studies in children should aim for achieving remission*	Absence of side effects could be accepted as secondary endpoint, but is not necessary to have it in guidelines. Strict steroid free remission is crucial in growing organisms. Accepted: As in adult patients, important secondary endpoint 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.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		without side effects on growth and maturation. Remission should be defined as clinical remission accompanied by endoscopic MH. *For induction/maintenance trials representative changes in mucosal appearance are expected, therefore endoscopy is required.* *Endoscopic MH and disease activity scores (similar to adults)* <u>with no evidence of side effects on growth, maturation, and bone mass</u> *should be used as co-primary end-points in clinical studies. Paediatric patient reported outcomes (pPRO) should be used as co-primary endpoint (instead of activity scores) as soon as a validated tool is available.* *Currently most used clinical indexes - the Paediatric CD Activity Index (PCDAI) and its modifications (e.g. wPCDAI) are not optimal for study purpose and the use of this index as the only* <u>co-</u>*primary endpoint for future studies is not recommended. However, until a fully validated pPRO is available, it may serve as a surrogate for symptomatic evaluation (and the evaluation of clinical remission).* *It also contains the parameter of growth velocity, which would have to be evaluated separately, if a validated pPRO is finally used. Improved growth pattern, height velocity beyond six months or finally normalised growth remains an important secondary endpoint in children.*	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	
11	7	Comment: Keywords Proposed change (if any): Inflammatory bowel disease and CDAI should be added in the list	Accepted
62	7	Comment: “Over the course of the disease, phenotype commonly changes from predominantly inflammatory disease to stricturing disease” Proposed change (if any): “structuring and/or penetrating disease”	Accepted
71	7	Comment: antibiotics have no major role in the treatment of Crohn disease Proposed change (if any): delete: “antibiotics (for colonic disease)”	Accepted
73	7	Comment: Nutritional support also has a role as primary therapy Proposed change (if any): Nutritional support also has a role as primary therapy in children	Accepted
98	7	Comment: Document seems to be focusing on luminal disease only Proposed change (if any): split up in luminal disease	Partly accepted. This has already been done. No changes necessary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		and fistulizing disease	
107	7	Comment: MRE has shown high accuracy for assessment of disease activity in the colon, and the MaRIA index, validated against endoscopy, has shown responsiveness to therapeutic interventioins. Proposed change (if any): delete “(small intestinal disease only)”	Not accepted. MRE has not been fully validated for measuring drug effects on mucosal healing. Thus, it cannot be recommended for evaluating drug effects in the colon where a direct method (endoscopy) is available.
130-131	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 and the reference to ECCO definition has been removed
133	7	Comment: It should be more precise: no response after completing an induction period of 6 -12 weeks of anti-TNF therapy. It would also be useful to suggest a definition for refractoriness to vedolizumab (e.g. no response after 14 weeks of treatment)	Partly accepted. It is not possible to provide precise definitions for all types of responses. The section has been revised to included general recommendations for defining these conditions.
136	7	Comment: CD in remission Proposed change (if any): split up in clinical remission and endoscopic remission	Accepted
138	7	Comment: absence of macroscopic signs of active inflammation is probably a too hard endpoint. It could be absence of ulceration according to SES-CD, which considers aphtae as ulcerative lesions Proposed change (if any): MH should be limited to absence of ulcers according to SES-CD	Accepted
174	7	Comment: “patient related outcomes”?	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): patient reported outcomes	
180	7	Comment: “response definition include response in terms of all parameters” it should be adapted to disease characteristics. Ileal CD has no diarrhoea, but intense pain. Number of stools cannot improve	Accepted
188	7	Comment on “remission free of steroids”: as for UC, this may be problematic for induction studies (i.e. insufficient time to achieve remission and withdraw steroids). In the induction part of the studies steroids should be maintained, because doses are different from maintenance (at least for biologics) and should be optimized for each stage (induction and maintenance)	Accepted
194	7	Comment on CDEIS score 0: it is not achievable. A score of 3 is more reasonable, and correlates with absence of ulceration. In UC the proposal is 0 – 1. Why should CDEIS be 0?	Accepted
203	7	Comment: Secondary endpoints Proposed change (if any): CD-related hospitalisation free survival should be considered as secondary endpoint	Partly accepted. The list of secondary endpoint cannot be exhaustive. Additional secondary endpoints may be included if adequately justified. This has been stated in the revised guideline.
213	7	Comment on “decrease in CDEIS of >5 points combined with a decrease of >2 points on a 5 point scale evaluating symptoms”: combined or assessed separately	Partly accepted. As the PRO’s have not been adequately validated, it is impossible (at this time) to make any recommendations in terms of response definitions. The recommendations have removed and replaced by a general remark about using response definitions according to the instruments used.
275-276	7	Comment on “(MRE is only suitable for small intestinal	Partly accepted. The remark is correct. The guideline has been

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		disease that cannot be evaluated by colonoscopy)": If some patients undergo MRE and other colonoscopy then the endpoints on healing can only be dichotomous: remission / non remission. Work is in progress to discuss with EMA the use of MRE as endpoint for healing, replacing endoscopy	revised to stress that until MRE has been fully validated as an instrument to measure drug effects on mucosal healing, the use of MRE is exploratory.
278	7	Comment: "In patients receiving steroids at entry, the medication should be tapered before evaluation of efficacy" This should be the case for maintenance of remission, but it is not realistic for induction of remission. In studies of active disease it is traditional to clamp the steroid dose at the entry level through to the primary end point to avoid the instability caused by steroid withdrawal	Accepted
282-283	7	Comment: minimal level of mucosal inflammation (e.g. a score >8 when using CDEIS or a score >6 when using SES-CD). Proposed change (if any): Corrections in CDEIS/SES-CD entry criteris should be made for patients with isolated ileal disease, to avoid exclusion of this subpopulation of patients	Accepted
295-298	7	Comment: It is stated that "clinical trials aiming at supporting a first line indication should always include comparison with the accepted first line treatment. However, later on it is pointed out that: 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.	Partly accepted. There is no contradiction. The placebo arm should be added in addition to the active comparator (i.e. the accepted first line treatment). The purpose of the placebo arm in this 3-arm study is to demonstrate assay sensitivity in a non-inferiority comparison between test drug and active comparator. The guideline has been amended to make this clearer.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		There seems to be a contradiction here (with the placebo inclusion/exclusion).	
312	7	Comment on Patients in remission: it should be remission or response (i.e. all patients who have a benefit from the drug). For example for anti-TNF therapy both response and remission at week 12 or 14 are predictors of remissioin at week 52. Remission at week 12 has higher specificity than response, but of course less sensitivity. It should be either remission or response	Accepted
322-323	7	Comment: It is pointed out that "for inclusion into maintenance studies patients are expected to have MH (e.g. SES-CD, CDEIS of 0)". However, this 0 score would be not feasible in most of the cases. In other words, the requisite to start maintenance treatment with 0 endoscopic score seems unrealistic. Proposed change (if any): SES-CD ≤3, or absence of ulcerations	Accepted
346	7	Comment: For operated patients, even more important than "clinical post-operative recurrence" is "endoscopic" recurrence (i.e. the gold standard), as it is more objective, more reliable, and has a clear prognostic value for predicting clinical recurrence. Proposed change (if any): the primary endpoint could also be endoscopic post-operative recurrence	Accepted
364-365	7	Comment on “clinical trials in patients with chronic, non-suppurative fistulas.”: This is not adequate. The main clinical manifestation of perianal fistulas is	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		drainage. It might be requested that patients have undergone proper surgical drainage complemented by a course of antibiotics, but allowing patients with draining fistulas into the trials is essential	
371	7	Comment on “demonstrate internal as well as external healing of fistulas.”: the problem is the MRI definition of fistula healing. We should seek advice from radiologists (e.g. Jaap Stoker, Jordi Rimola). In addition, absence of abscess should be included in the definition of healing	Accepted
420-421	7	Comment: the sentence should read active Crohn’s disease and not newly diagnosed disease, as EEN can be used for treatment of relapses at follow up and not just at diagnosis	EEN is mainly used in naïve Crohns patients, in other cases is less effective.
438	7	Comment: UC Proposed change (if any): CD	Actepted
441	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	Antropometric parameters are basic criteria for any study in pediatric age, including extrapolation, specific GL update is not considered necessary
469	7	Comment: Several large recent pediatric cohorts show that the ileal intubation rate in children with CD is only 75-80% (but caecal intubation is >93%). Because of these findings it is suggested that in the 20-25% of children without ileal intubation, the SES-CD for that segment will be imputed from MRE. Otherwise the primary outcome cannot be calculated for a substantial portion of the included patients.	Complete endoscopy and MRE are part of combined outcomes for evaluation of any IBD patient…

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
471	7	Comment: MRE may be even more relevant for the paediatric population	It is as preassumption in our text
483-484	7	Comment on “MRE is preferable to computed tomography enterography (CTE) in children due to considerable X-ray exposure of CTE”: MRE should be considered as an alternative to endoscopy.	Not accepted, MRE is not alternative to endoscopy
494-497	7	Comment: Adequately powered non-inferiority design is not feasible in children given the big sample size needed Proposed change (if any): a wider inferiority margin than otherwise desired can be accepted without placebo	The right choice of development strategy depends on multiple factors such us availability of adult data, class of products and other pediatric indications data.
501-502	7	Comment: the sentence is not clear. 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.	agreement
Line 106	8	Comment: I have concerns on the limitation of MR enterography to small bowel assessment. MRI has shown high accuracy for assessment of disease activity in the colon. In addition, the MaRIA index (an MR index of activity and severity for luminal Crohn’s disease), validated against endoscopy, has shown responsiveness to therapeutic medical interventions. Proposed change (if any): delete “small intestine only”	Not accepted. MRE has not been fully validated for measuring drug effects on mucosal healing. Thus, it cannot be recommended for evaluating drug effects in the colon where a direct method (endoscopy) is available.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
132-133	8	Comment:Definition of Refractory Crohn's disease should be more precise Proposed change (if any): Patients are refractory to anti-TNF therapy if they make no initial response after completing an induction treatment period of 6-12 weeks to appropriate doses/duration of anti-TNF therapy	Partly accepted. It is not possible to provide precise definitions for all types of responses. The section has been revised to included general recommendations for defining these conditions.
174	8	Comment: patient related outcome is incorrect term Proposed change (if any): patient reported outcomes (PRO)	Accepted
276-277	8	Comment: again, MRE cannot be limited to small bowel assessment. MRE can also assess the colon after its optimal preparation. The use of MRE instead of endoscopy may carry a number of advantages in clinical trials (see my general comments above) Limitations of MRE is low sensitivity for detecting mild inflammatory lesions that in clinical trials has minimal impact Proposed change (if any): delete "(MRE is only suitable for small intestine disease that cannot be evaluated by colonoscopy)"	Not accepted. MRE has not been fully validated for measuring drug effects on mucosal healing. Thus, it cannot be recommended for evaluating drug effects in the colon where a direct method (endoscopy) is available.
284	8	Comment: The MaRIA score >11 has a high sensitivity and specificity (around 95%) for detecting ulcerations, and represents a valid alternative to endoscopy indexes (CDEIS/SES-CD)	Not accepted. At the present time, this instrument is not been validated to an extent which would allow MRE/MaRia to used as the sole instrument for assessing efficacy in phase 3 studies.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): include MaRIA score (with appropriate cuttofs) as alternative to CDEIS/SES_CD	
324	8	Comment: Typo mistake (?) CDAIS Proposed change (if any): CDEIS instead of CDAIS	Accepted
324-325	8	Comment: Add MaRIA <7 (absence of inflammation) score as additional remission criteria	Not accepted. Please see above.
364	8	Comment: differentiate luminal from perianal fistulising CD Proposed change (if any): Treatment of fistulising perianal CD	Accepted
368	8	Comment: close fistulas and maintain their closure is referred as deep fistula healing	Accepted
372-373	8	Comment: MRI may detect collections, as well as fistula extensions, that has impact on clinical management before including patient in clinical trials. So that, MRI should be included in the baseline assessment, which is not clearly stated in the draft Proposed change (if any): Currently magnetic resonance imaging (MRI) is the recommended technique to assess baseline inflammation and complications and to demonstrate internal as well as external healing of fistulas	Accepted
382	8	Comment: short-term trials may overestimate the benefite of drugs. Evidence indicates that after 8-12 w of treatment, there is external opening closure but persisting fistula activity demonstrated by MRI. Early clinical response was not associated with radiological	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		healing. Demonstration of complete fistula healing requires longer treatment (at least 12 months). Therefore, long term trials using pelvic MRI are recommended	
219	9	Comment: “Proportion in Steroid-free remission” is given as an example of steroid sparing effect. The co-primary endpoints, however, include “symptomatic 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). 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 example has been qualified as only relevant when the primary endpoint does not include “steroid free”.
295-298	9	Comment: For non-inferiority studies, a placebo arm is suggested to establish assay sensitivity. It should be acknowledged that a placebo arm is not the only way to demonstrate assay sensitivity. It would also be helpful to clarify if any formal statistical inference vs placebo is expected if such a 3-arm design is adopted.	Partly accepted. It is stated “preferably” which means that other means of documenting “assay sensitivity” may be used. No change necessary. A placebo arm can only document assay sensitivity if superiority of the test drug against placebo is demonstrated. This is discussed in ICH E10. No change necessary.
299-301	9	Comment: For on-add design where the test drug (T) is compared to add-on placebo (P), a third arm (anti-TNF; R) is mentioned. Such a trial would certainly need to establish the superiority of T versus P. It would be helpful to clarify if there is any expectation on the T:R and/or R:P comparisons.	Partly accepted. The section has been rewritten
60	9	Comment: Free perforation and abscess formation are	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		examples of penetrating disease that do not necessarily make a fistula. Proposed change (if any): “Fistulizing” disease should be replaced by “penetrating” disease.	
220	9	Comment: reduction in surgical visits is an absolute secondary endpoint but with multiple treatment options now available we should also consider rates of hospitalization, ER visits and use of CT/MR imaging Proposed change (if any): Add Hospitalizations, ER visits and use of CT/MR imaging	Partly accepted. The list of secondary endpoint cannot be exhaustive. Additional secondary endpoints may be included if adequately justified. This has been stated in the revised guideline.
287	9	Comment: care must be taken to avoid infectious diarrhoea. We should add bile salt diarrhoea and irritable bowel syndrome Proposed change (if any): sentence should read “Shorter duration of disease has to be justified and care must be taken to avoid inclusion of patients with infectious and bile salt diarrhoea as well with irritable bowel syndrome”.	Accepted