European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON THE DEVELOPMENT OF NEW MEDICINAL PRODUCTS FOR THE TREATMENT OF CROHN'S DISEASE

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	**Schering-Plough**	
2	**BIOGEN IDEC**	
3	**Bristol -Myers Squibb Company**	
4	**CENTOCOR BV**	
5	**EFPIA**	
6	**ECCO- European Crohn's and Colitis Organization**	

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Table 2:Discussion of comments

COMMENTS FROM SCHERING-PLOUGH		
SPECIFIC COMMENTS ON TEXT		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
Page 4/8, Paragraph 3.1, "Disease stages to be studied"	"Patients showing signs and symptoms with evidence of active inflammation well defined by biological criteria (CRP, ESR) over a period of three to six months despite treatment can be divided into 2 categories." CRP is a recognized marker of inflammation; however, some patients show signs of active inflammation even though their CRP is not elevated. These patients should not be excluded from participating in clinical trials. ESR is even a more tentative marker. In addition, there may be other markers that could be more predictive or other criteria which would be more relevant. We suggest the wording be more open to reflect further/future scientific development.	Recommend the following edits/additions in italics: "Patients showing signs and symptoms with evidence of active inflammation *which may be corroborated* by biological criteria, *such as* CRP, *and/or other clinical markers* over a period of three to six months despite treatment *may* be divided into 2 categories." Agreed. The wording has been changed.
Page 4/8, Paragraph 3.2, "Crohn's Disease in remission-Potential Claims":	Last line, "Other claims such as steroid sparing, treatment of abscess, endoscopic remission, treatment of obstruction and improvement in quality of life should not form a part of the indication." These other effects provide significant benefits and are of important value to patients, and as such, when appropriately demonstrated, may legitimately form part of the indication. If not part of the indication, they should at least be allowed to appear in the prescribing information in another appropriate section of the labelling, such as section 5.1 of the SPC	Recommend the following edits/additions in italics: "Other claims such as steroid sparing, treatment of abscess, endoscopic remission, treatment of obstruction and improvement in quality of life *might* form a part of the indication, *or as appropriate, be included in other relevant section(s) of the prescribing information*." Partly agreed. The wording has been changed.
Page 4/8, Paragraph 3.2, "Potential Claims"	Under Potential claims it is noted that the potential indications include…/induction of remission AND Maintenance of remission/… While induction of remission and maintenance of remission is the preferred treatment outcome, achieving response is also important in this disease. Induction of response and maintenance of response bring significant value to patients and should be included as potential	Recommend the addition of the text in italics: The principal aims of management of Crohn's disease and thus, potential indications are: • Induction of response, maintenance of response • Treatment of active disease/Induction of remission

	indications.	• Maintenance of remission/Prevention of relapse • Treatment of fistulizing Crohn's disease Not agreed. Goal of treatment is induction of remission
Page 4/8 Paragraph 4.1.1 "Patients to be included"	Last 2 lines…"Depending on the aim of the treatment, it is recommended that patients included in the trials should have active disease as determined by a CDAI score of at least 220. Dependent on the place of drug in the therapeutic arsenal a CDAI score of at least 250 may be appropriate in some cases." There is no mention of CDAI scores for severe disease. Severe disease is usually defined as a CDAI<450, however, some trials considered patients with a CDAI<300 to have severe disease, if they had been on co-medication of steroid and/or immunosuppressants. The guidance should note that other definitions of disease state beyond active disease may be appropriate, and such definitions should be appropriately justified in light of the target patient population, including in relation to background medications, or consideration to failed prior therapy.	Recommend the following addition in italics: "*The use of other CDAI scores, or definitions of disease states (e.g., for severe Crohn's Disease) may also be used, when appropriately justified. Use of CDAI scores may be dependent on other factors relevant to the patient population studied, such as background medications or consideration of failed prior therapy.*" Partly agreed. The wording has been changed.
Page 5/8, Paragraph 4.1.4 – Response Variables… Primary Endpoints	First line, "The proportion of patients achieving remission within the period of about eight weeks is an appropriate primary end-point to justify short-term treatment of active Crohn's disease" '…is an appropriate primary endpoint…'restricts the selection of a primary endpoint while other primary endpoints may be more appropriate depending on the desired outcome of the study. Additional flexibility should be reflected in this statement.	Recommend the addition of the following text (in italics): "The proportion of patients achieving remission within the period of about eight weeks is an appropriate primary end-point to justify short-term treatment of active Crohn's disease. *Other end points, when appropriately justified, may also be appropriate.*" Not agreed. Remission is the clinically relevant primary endpoint.
Page 5/8, Paragraph 4.1.4 Secondary Endpoints	In secondary endpoints … Other relevant endpoints should be included in this section such as "mucosal healing", as well as other health economic outcomes, besides the IBDQ, such as reduction in hospitalization and surgery. We suggest that the option to identify/use other relevant endpoints be included in the guideline.	Recommend the addition of the following text under Secondary Endpoints: • *Mucosal healing* • *Reduction in hospitalization and surgery* • *IBDQ or other appropriate health economic outcomes* • *Other secondary endpoints, when appropriately justified* Partly agreed. The wording has been changed
Page 5/8, Paragraph 4.1.4 response	There is no need to change the response criteria from 70 to 100 CDAI reduction (and a consequence of raising the limit to 100 would be that active disease should be at least 250 at baseline because otherwise a 70 point reduction would bring a patient with baseline CDAI 220 into	Recommend the following edit in italics: "A patient is called a responder, if remission has been achieved or a reduction of at least ***70*** in CDAI has been observed at the end of the treatment period." Not agreed. A reduction of 100 points is considered appropriate to define a

Variables	remission without fulfilling the response criteria)	clinically relevant response and to discriminate responder to test drug from placebo responders.
Page 5/8, Paragraph 4.1.4 response Variables	Primary Endpoint: Primary endpoint of remission is stated at about 8 weeks, but recent trials used earlier time points.	Guideline should state if 4 to 8 weeks is acceptable for induction of remission. Agreed. The wording has been changed
Page 6/8, Paragraph 4.2.5. Study duration	The guideline recommends a follow-up period of 3 months after treatment discontinuation.	Guideline should clarify the purpose of this follow-up period, i.e. to address time to loss of remission/response or safety? This has been clarified.
Page 7/8, Paragraph 4.3, Treatment of fistulizing Crohn's disease	The importance of MRI closure compared to external closure, improved PDAI has not been well defined	The clinical benefit of fistula treatment is better reflected by PDAI, which should be the primary endpoint, whereas MRI should serve as a secondary endpoint. Not agreed. MRI is currently the recommended technique to demonstrate fistula healing.

COMMENTS FROM BIOGEN IDEC

GENERAL COMMENTS

Thorough Guidance on the development of new medicinal products for the treatment of Crohn's disease. Central comment is that since response is now recognized as a decrease in 100 or more points in the CDAI (not 70 as in the previous points to consider document), believe it is reasonable to now consider as a potential claim for the treatment of active disease induction of response in addition to induction of remission. Similarly it makes sense to have as a maintenance claim, maintenance of response/prevention of relapse. Lastly suggest that 6 months of preventing relapse is sufficient for a maintenance of remission (response) claim rather than requiring 12 months.

Not agreed. Remission is still the preferred primary endpoint. For inflammatory bowel disease it is considered appropriate to evaluate the effect over at least 12 months.

SPECIFIC COMMENTS ON TEXT

Line no. + paragraph no.	Comment and Rationale	Proposed change (if applicable)

Page 4, section 3.2, line 2	Add treatment of active disease should include induction of response where response is a decrease in CDAI of at least 100 points. A 100 point decrease in CDAI is a clinically meaningful benefit to patients with Crohn's disease	Add Treatment of active disease/Induction of response Not agreed. Goal of treatment is induction of remission.
Page 4, section 3.2, line 3	Similarly maintenance of response (CDAI drop of at least 100) should be considered a clinically significant maintenance claim	Add Maintenance of response/Prevention of relapse Not agreed. Goal of maintenance treatment is maintenance of remission.
Page 5, section 4.1.4, lines 5 and 6	Definitions of Crohn's disease severity, mild activity (CDAI 150-219), moderate activity (CDAI 220-450), and severe activity (CDAI >450) do not correlate with the approved label for infliximab. Studies of infliximab did not investigate subjects with a CDAI greater than 450, yet the indication is for severe Crohn's disease. How does the Agency reconcile these differences	This has been clarified.
Page 5, section 4.1.4, line 11	Under Primary Endpoint, suggest providing a range of suitable time period in which to expect a clinical endpoint rather than stating about 8 weeks. Placebo rates in Crohn's disease dramatically increase from 4-8 weeks, and selecting 8 weeks may be too far out to demonstrate an effect size.	Suggest changing "… within the period of about eight weeks…" to within a range of 4 to 10 weeks…" Agreed. The wording has been changed.
Page 5, section 4.1.4, line 20	Assessment of endoscopic healing, the CDEIS is suggested as an example. Another much easier score has been developed, the SESCD (simplified endoscopic score in Crohn's disease) that has been shown to correlate with the more cumbersome CDEIS	Suggest adding in "… (CDEIS) simplified endoscopic score in Crohn's disease (SESCD). The suggestion to use the traditional CDEIS does not exclude use of the simplified score
Page 6, section 4.1.4, line 3	Agree with possible benefit of stratification by disease activity, but not disease location. Many studies of different systemically delivered agents have not demonstrated a notable benefit by disease location.	Remove "...disease localisation… " from the sentence Agreed. The text has been amended.
Page 6, section 4.1.5, line 3	Be more specific on requirements for study duration for treatment of active disease/Induction	Suggest durability of remission/response as 2-3 months Not agreed. The text is specific enough regarding duration of treatment.
Page 6, section 4.2.4 line 2	Duration of maintenance of remission is clinically meaningful at 6 months; therefore requiring 12 months is excessive...	Suggest changing "… no surgery needed throughout at least 6 months." Not agreed. For inflammatory bowel disease it is considered appropriate to evaluate the effect over at least 12 months.

COMMENTS FROM Bristol -Myers Squibb Company		
SPECIFIC COMMENTS ON TEXT		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
Section 3.1, Paragraph no. 4	In the definition of Refractory Crohn's Disease, patients refractory to methotrexate (lack of response to a sufficient dose within 3-6 months) should also be considered as having Refractory Crohn's Disease based on the demonstrated efficacy of methotrexate[1].	Proposed change of statement from "Patients are refractory to azathioprine/6-mercaptopurine if they do not respond to a sufficient dose within 3 to 6 months" to "Patients are refractory to azathioprine/6-mercaptopurine/methotrexate if they do not respond to a sufficient dose within 3 to 6 months" Not agreed. Treatment with MTX in Crohn's disease is less established compared with AZA.
Section 4.2.1	Section 4.2.1 states that patients to be included for study of maintenance of remission/prevention of relapse are those "*who are in remission as defined by a CDAI of <150 for at least one month*". The criteria stated for entry into maintenance studies is not consistent with clinical practice and can present significant limitations for clinical study design and conduct. Clinical response as defined by CDAI reduction of 70 or 100 points from baseline has been shown to be clinically meaningful by its correlation in multiple clinical studies to the objective assessment of mucosal healing[2] as well as patient's subjective assessment by Inflammatory Bowel Disease Questionnaire (IBDQ)[3]. The clinical significance of clinical response in the clinical practice setting is also reflected in that if a subject achieves response to a therapy, even if not at the level of remission as per proposed definition in the CHMP guideline, the subject is likely to be considered for continuation of therapy. From an ethical standpoint also, it is not appropriate to discontinue a therapy that has induced a	Change of statement from "Patients who are in remission as defined by a CDAI of <150 for at least one month may be included into the trials" to "Patients who are in remission as defined by a CDAI of <150 and patients who are in clinical response as defined by a CDAI reduction of greater than or equal to 100 points from baseline may be included into the trials." Partly agreed. Patients in response can be considered for enrolment into maintenance phase of combination studies although preferably only patients in remission should be entered.

[1] Feagan BG, Rochon J, Fedorak RN, et al. Methotrexate in the treatment of Crohn's disease. N Engl J Med 1995;332:292-7.
[2] D'Haens G, Deventer SV, Hogezand RV, Chalmers D, et al. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: a European multicenter trial. Gastroenterology 1999;116:1029-1034.
[3] Feagan BG, Yan S, Bala M, et al. The effects of infliximab maintenance therapy on health-related quality of life. The American Journal of gastroenterology 2003;98(10):2232-2238.

	clinical response. Recent precedents based on the maintenance trials conducted thus far by other biologic compounds (2 of which have been approved and 2 are under review), have included subjects in clinical response at the end of induction therapy. [4,5,6,7] The inclusion of only subjects who are in maintained remission into maintenance study will require a prohibitorily large sample size of patients to enter the study. The rate of remission seen in the biologic compounds, at a single time point at the end of induction, ranged between 36-48%. The rate of remission and hence the proportion of subjects allowed to enter the maintenance trial, if defined by remission over at least one month, is expected to be even lower.For the reasons presented above, we propose that all subjects who achieve clinical response should be allowed to enter maintenance studies.	
Section 4.2.4	Maintenance of remission and Prevention of relapse are listed as potential indications in Section 3.2. However, Section 4.2.4 (in contrast to what is stated in Section 3.2) does not state the proportion of patients in whom relapse of disease is prevented as a primary end-point.	Propose inclusion of the proportion of patients in whom relapse of disease is prevented over 12 months as a primary end-point under Response Variables. Not agreed. Only one primary endpoint is proposed, reflecting the proportion of patients who stay in remission (i.e. without relapse).

COMMENTS FROM CENTOCOR BV

SPECIFIC COMMENTS ON TEXT

Line no. + paragraph no.	Comment and Rationale	Outcome

[4] Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT 1 randomized trial. Lancet 2002;359:1541-1549.
[5] Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007;132:52-65.
[6] Schreiber S, Khaliq-Kareemi M, Lawrance I, Thomsen O, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. N Engl J Med 2007;357:239-50.
[7] Sandborn WJ, Colombel JF, Enns R, Feagan BG, et al. Natalizumab induction and maintenance therapy for Crohn's disease. N Engl J Med 2005;353:1912-25.

Section 4.1.4 **Paragraph 1**	Though remission is the primary goal of therapy, attainment of a clinical response defined as a ≥100-point decrease in the CDAI may be a more appropriate endpoint in certain circumstances. Selection of a primary efficacy endpoint should be primarily determined by the efficacy profile of the drug being evaluated. For example, consider the case of a hypothetical drug for treating lung cancer: though the therapeutic goal is cure (100% 5 year survival), the drug is curative in <1% of patients whereas it prolongs survival by 6 months in 50% of patients. Hence, the prolongation of survival is the most appropriate endpoint for a clinical trial as it conveys the most clinically relevant information to the physician. Though remission is the ideal treatment outcome in Crohn's disease, clinical response is a clinically relevant endpoint for the assessment of therapeutic efficacy and clinical response provides information on 2-3 times as many patients as clinical remission (Sands BE, Steinhart HA, Lewis JD, et al. Optimal Crohn's disease activity index (CDAI) response criteria is defined by decrease greater than or equal to 100 points. *Gastroenterology*. 2003;124(suppl 1):A-206). Furthermore, clinical response is a clinically relevant outcome associated with mucosal healing, the elimination or reduction of corticosteroids, and the reduction in the number of hospitalizations and surgeries in patients with moderately to severely active Crohn's disease (Daperno M, D'Haens G, Van Assche et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointestinal Endoscopy. 2004;60:505-512; D'Haens G, Van Deventer S, Van Hogezand R et al. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: a European multicenter trial. *Gastroenterology*. 1999;116:1029–1034; Rutgeerts P, Feagan B, Lichtenstein G, et al. comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* 2004;126:402–413). Furthermore, physicians continue to treat patients who have responded, but have not attained remission. Therefore, because the response endpoint provides clinically relevant information on treatment outcome in significantly more patients relative to the	Provide flexibility in choice of primary endpoint to include response (CDAI decrease of ≥ 100) as well as remission. The primary endpoint should be clinically relevant and reflect efficacy profile in substantial proportion of patients. An endpoint that reflects clinically relevant efficacy in a substantially greater proportion of the patient population should be preferred over an endpoint that reflects efficacy in only a minority. Not agreed. Goal of treatment is induction of remission

	remission endpoint it is the most appropriate endpoint for use in trials of novel therapies in Crohn's trials. Another consideration in the choice of primary endpoint is whether the test drug is being evaluated for first, second, third line or last line therapy. For last line therapy in patients with severe disease, who have failed steroids, immunosuppressives and anti-TNF therapy, and for whom there are essentially no other viable medical therapeutic options an agent that induces a clinical response would be extremely important.	

Section 4.1.4 **Paragraph 2** **Primary endpoint**	**The timing of the primary end-point needs to reflect the efficacy profile of the test agent and be chosen to optimize differentiation from placebo. This is particularly important for therapies for which there are potential safety concerns and a prolonged duration of action:- clinicians require early efficacy assessments so that ineffectual therapies can be stopped.** Crohn's symptoms and signs tend to be cyclical and cyclical conditions are characterized by delayed placebo responses:- this may be the reason for the increasing placebo response after 6 weeks that has been seen in recent trials of various therapies. Optimal differentiation from placebo is best achieved with endpoints at 4-6 weeks (Su C, Lichtenstein GR, Krok K, et al. A meta-analysis of the placebo rates of remission and response in clinical trials of active Crohn's disease. *Gastroenterology*. 2004;126(5):1257-1269).	Allow flexibility of timing of primary endpoint assessment between 4-6 weeks. Agreed. The text has been amended.
Section 4.1.4 **Paragraph 2** **Secondary endpoints**	**For patients with severe disease who have failed steroids, immunosuppressives and anti-TNF therapy, with essentially no other viable medical therapeutic options, withdrawal/decrease of steroids may be clinically beneficial even for those who are not proven to be steroid-dependent. In addition, to be steroid-free and in remission may be of significant clinical benefit in a refractory population who have failed steroids, immunosuppressives and anti-TNF therapy, and for whom there are essentially no other viable medical therapeutic options.**	Allow flexibility around the secondary endpoints to (1) include patients who are on steroids at baseline but are not necessarily proven to be steroid-dependent and (2) consider steroid-free and in remission for ≥90 days after withdrawal of test drug to be a potentially significant outcome; (3) in a refractory population, an endpoint of clinical remission at 1 year and not receiving corticosteroids may also be clinically meaningful particularly in this clinical setting. Partly agreed. Patients receiving steroids baseline without being steroid refractory can be included. Steroid free remission is a relevant goal and the text has been amended.

Section 4.2.1 **Paragraph 1**	An extension of the point previously made concerning consideration of the choice of primary endpoint for first, second, third line or last line therapy. Since for last line therapy in patients with severe disease, who have failed steroids, immunosuppressives and anti-TNF therapy, with essentially no other viable medical therapeutic options, an agent that induces a clinical response (CDAI decrease of ≥100 points) would be extremely important. Hence, it would be appropriate to enroll such patients in a maintenance study in order to evaluate that their response is maintained. In addition, practicing physicians will most likely decide whether patients are in clinical remission (or response) following a single clinical evaluation before initiating maintenance therapy: they are very unlikely to wait a month, particularly in a refractory patient population.	**Allow flexibility to enroll patients with clinical response into maintenance study and not require that such patients be in response (or remission) for 1 month prior to the initiation of maintenance therapy.** Consider adding maintenance of clinical response as a potential indication (section 3.1). Partly agreed. Patients in response can be considered for enrolment into maintenance phase of combination studies although preferably only patients in remission should be entered. The primary endpoint for the induction phase should be remission.

COMMENTS FROM EFPIA

GENERAL COMMENTS

EFPIA welcomes the updating of the guidance on Crohn's Disease. Overall, the document provides useful information to guide the development of medicinal products for the treatment of Crohn's Disease. However, there are a number of points of concern highlighted in the following sections.

KEY COMMENTS

Key comments:

- Crohn's disease is a continuously active disease and as such the same patients can be used to study both remission and relapse. This is stated in section 4.2.1 of the guidance however the continuous nature of Crohn's disease should also be clearly stated in the introduction to this guidance.

Agreed. A sentence has been added.

- The biomarkers of inflammation (such as CRP and ESR) do not correlate well with the clinical expression of active disease in individual patients and their use for diagnosis is not currently justified. As currently written the guideline use the biological criteria (CRP and ESR) to define evidence of active inflammation in active Crohn's disease. It is strongly felt that the guideline should be amended to include patients without elevations in these measures who have clinical evidence of activity present.

Agreed. The wording has been changed.

- Steroid sparing should be able to form part of the indication statement if this is the population which has been studied in clinical trials. Further, in section 4.1.4

the primary endpoint for trials looking at the withdrawal or decrease of the use of steroids in steroid dependent patients is discussed. As this is important information for a drug being developed for use in steroid dependent patients this should be reflected in the indication statement.

Not agreed. Although it is agreed that steroid sparing is an important goal in treatment of Crohn's disease, it is generally not accepted that this should form part of the indication e.g. considering that the new treatment may have other harmful AEs, known or not known at the time of market approval.

- The potential claims currently listed exclude patients who may derive significant benefit but not actually achieve clinical remission (i.e. a responder population at the severe end of the disease spectrum). There will be some patients who fail to achieve remission on all therapies despite adequate dosage and duration and if their symptoms do improve then this is clinically meaningful especially if this is a reduction in stool numbers and blood loss.

Not agreed. Goal of treatment is induction of remission.

- The guidance does not give consideration to patients with milder active disease (CDAI > 150 but < 220). Depending on the profile/mechanism of the agent under study, this may be the appropriate patient population for inclusion in the study and should be addressed in this guidance.

Not agreed. It may be difficult to separate mild symptoms of Crohn's disease from IBS. Generally, it is considered that effect in these patients would be difficult to distinguish from placebo response. Therefore not recommended.

- The approvability for a first-line indication should be based on the balance of both benefit and risk. As such it should also be possible for a new drug which has been demonstrated to be less effective than the current standard of care (steroids) but with an improved safety profile to be approved for a first-line indication.

The issue is outside the scope of this Guideline

SPECIFIC COMMENTS ON TEXT

Line no+ paragraph no.	Comment and Rationale	Proposed change (if applicable)
Section 1, paragraph 1, line 1	Crohn's disease is a continuously active disease. It is important to accurately reflect the continuous nature of this disease, particularly as many of the same drugs are used for both remission and maintenance.	Change to: 'Crohn's disease is a chronic continuously active inflammatory disease of the gastrointestinal tract, with relapsing and remitting clinical course, the cause of which remains unknown.' Agreed. A sentence has been added
Section 1, paragraph 1, line 2	Add full stop at end of first sentence	Change to: '…cause of which remains unknown.' Agreed.
Section 1, paragraph 2, line 2	Replace comma with full stop at end of first sentence	Change to: '…and the exclusion of alternative disease states.' Agreed.
Section 1,	Major symptoms: This should include bleeding and fatigue but not weight loss. As weight loss is only seen in those patients	Change to: 'The major symptoms are diarrhoea, abdominal pain, bleeding and fatigue. Physical findings, including evidence of anaemia, reflect the site and

paragraph 3, line 3	with severe disease or with malabsorption, usually from ileal resection. Physical findings: This should include evidence of anaemia. Also it is referred rebound tenderness that is the sign suggesting serosal inflammation and not abdominal tenderness directly over such a mass. This needs to be made in clear in the text.	severity of the pathology. Referred rebound tenderness suggests serosal inflammation. Perianal manifestations are common.' Not agreed. Weight loss may be present as a general marker of disease even in Crohn colitis, although the pathophysiology behind weight loss is different than from malabsorption in small bowel disease.
Section 1, paragraph 4, line 1	Antibiotics are only used for infectious complications and so should not be listed a primary medical therapy. Symptomatic drugs, such as antidiarrhoeals and antispasmodics, should also be listed.	Change to: 'Medical therapy includes corticosteroids, immunosuppressant drugs, anti-TNFα agents, symptomatic drugs such as antidiarrhoeals and antispasmodics.' Not agreed. Antibiotics are used in Crohn's colitis even without infectious complications. The list of symptomatic treatment that does not target CD per se could be very long and for sake of reducing the text burden is left out.
Section 3	It is suggested that a section addressing the potential and value of disease-modifying Medicinal products is added.	The following text should be added: 'While there are no existing examples of therapies that are considered "disease modifying" for Crohn's Disease, it is possible that future therapies will successfully address this medical need, and the significant medical value of such potential therapies is recognised. A consensus working definition of disease modifying therapy in CD is not currently available. However, sponsors are encouraged to explore potential disease-modifying medicinal products based on an understanding of the natural history of CD and including clear demonstration of alteration of disease path and clinical outcome. Future examples of therapeutic approaches that demonstrate evidence of disease modification may contribute to the development of additional working definitions and guidance.' Not agreed. Considered out of the scope of this guidance.
Section 3.1, paragraph 2, line 2	Clinical expressions of active disease do not correlate well with biomarkers of inflammation (such as CRP and ESR) in individual patients. The Montreal Working Party (2005) concluded that 'the use of these markers for diagnosis is not currently justified, given the limited sensitivity of available markers' (Satsangi J et al, Gut: 2006; 55, 749). Thus the use of such measures of inflammation should be considered 'exploratory' until more information is available. Patients without elevation of these laboratory values should also be	Change to: 'Patients showing clinical signs and symptoms with or without evidence of active inflammation (defined by biological criteria, e.g., CRP, ESR) over a period of three to six months despite treatment can be divided into 2 categories. Agreed. The sentence is rephrased.

	considered for inclusion into clinical trials if clinical evidence of activity is present. The biomarkers should be supportive.	
Section 3.1, 1st bullet point	Steroid dependent CD: It should be clarified whether steroid dependent patients, who, by definition would not have active disease while on steroids, would be eligible for enrolment in studies in active disease.	It is considered that the text concerning steroid dependent patients is already clear enough. Preferably steroid dependent patients, well defined, should be studied in separate studies.
Section 3.1, 1st bullet point, line 1	Steroid dependent CD should include patients on azathioprine as well as those on steroids alone, as the combination is frequent used.	Change to: 'Patients who respond to steroids but whose disease flares on tapering (precluding steroid withdrawal) and those on azathioprine in combination with steroids are classified as steroid dependent.' Not agreed. Even though the combination is usual, steroid dependency is referring only to the fact that the patients relapses when steroids are tapered and withdrawn.
Section 3.1, 1st bullet point, line 4	'Merely the use of corticosteroids at baseline is not equal to steroid- dependency.' is a confusing and misleading sentence. The use of steroids at baseline may indicate dependency if previous efforts to taper use have been unsuccessful. This sentence should be reworded to avoid ambiguity.	Change to: 'The use of corticosteroids at baseline is not equal to steroid-dependency, unless previous attempts to taper steroid use have proved unsuccessful.' Agreed. The sentence is rephrased.
Section 3.1, 2nd bullet, line 3	At least an example of an adequate dose and duration of treatment for corticosteroids before a patient can be classed as steroid refractory should be given.	Not agreed. Specific cut-off cannot be provided within the Guideline. Any definition has to be justified by consensus documents.
Section 3.2, 1st and 2nd bullet points	The treatments for active disease/induction of remission, and the treatments for maintenance of remission/prevention of relapse are largely the same and this should be reflected in this guideline.	Insert: 'The treatment of active disease/induction of remission, and the treatment for maintenance of remission/prevention of relapse may be the same. Therefore it is possible that some clinical trials may support an approval of both acute and maintenance treatment.' after the list of bullet points. Agreed. Sentence has been added.
Section 3.2, paragraph 5, line 1	Steroid sparing should be able to form part of the indication statement if this is the population which has been studied in clinical trials. In section 4.1.4., the primary endpoint for trials looking at the withdrawal or decrease of the use of steroids in steroid dependent patients is discussed. As this is important information for a drug being developed for use in steroid dependent patients this should be reflected in the indication statement.	Change to: 'Other claims that could be considered on a case by case basis include steroid sparing and refractory patients. Claims such as treatment of abscess, endoscopic remission, treatment of obstruction and improvement of quality of life should not form part of the indication.' . Not agreed. Although it is agreed that steroid sparing is an important goal in treatment of Crohn's disease, it is generally not accepted that this should form part of the indication e.g. considering that the new treatment may have other

		harmful AEs, known or not known at the time of market approval.
Section 3.2.	The potential claims currently listed exclude patients who may derive significant benefit but not actually achieve clinical remission (i.e. a responder population at the severe end of the disease spectrum). There will be some patients who fail to achieve remission on all therapies despite adequate dosage and duration and if their symptoms do improve then this is clinically meaningful especially if this is a reduction in stool numbers and blood loss.	The following text should be added: 'The proposed indication of treatment of Crohn's disease/induction of remission includes the responder population that have not achieved remission.' Not agreed. Remission is the goal of treatment and the preferred primary endpoint.
Section 4	It would be useful if the number of studies required for approval were given. Two induction studies and one maintenance study should be sufficient for the following reasons: • Experience with treatments approved for Crohn's Disease to date shows that the efficacy in inducing remission is predictive of efficacy in maintaining remission. • The Crohn's disease patient population is small compared to other diseases so the requirement for multiple trials is difficult to fulfil, especially for maintenance trials. Patients need to achieve remission, usually in the induction trial with the same investigational drug, to be eligible for the maintenance trial. As only a fraction of patients completing the induction of remission study will be eligible for the maintenance trial, the induction study needs to include a higher number of patients than necessary to sufficiently power the maintenance study. If only one maintenance trial is required, patients from two induction studies can be enrolled into the one maintenance study which would provide a sufficiently large sample size.	The following text should be added: Two confirmatory induction of remission trials and one maintenance of remission trial are usually sufficient to prove the efficacy and safety of the test drug. Not agreed. Requirements follow general rules for all new active substances.
Section 4.1.1, line 4	Many patients may not have an established disease phenotype even with a minimum time from diagnosis of 3 months.	Change to: 'The minimum time from diagnosis should be at least 3 months at inclusion *if possible.* Not agreed. It is important that diagnosis is confirmed prior to inclusion into a clinical trial.

Section 4.1.1, line 6	'Dependent on the place of drug in the therapeutic arsenal a CDAI score of at least 250 may be appropriate in some cases.' Active disease should be defined as a CDAI score of 220 or greater. The place of the drug in the therapeutic arsenal should not be determined ahead of the Phase 3 program, but rather should be determined as a result of the risk/benefit assessment in the MAA.	Partly agreed. For treatments that may have known or unknown serious side effects it is important to include patients with a more serious disease to be able to make a proper benefit/risk assessment in this population. The indication reflects the study population.
Section 4.1.1.	The guidance does not give consideration to patients with milder active disease (CDAI > 150 but < 220). Depending on the profile/mechanism of the agent under study, this may be the appropriate patient population for inclusion in the study and should be addressed in this guidance.	Not agreed. It may be difficult to separate mild symptoms of Crohn's disease from IBS. Generally, it is considered that effect in these patients would be difficult to distinguish from placebo response. Therefore not recommended.
Section 4.1.2, paragraph 1, line 1	Randomised double-blind parallel group trials are appropriate for confirmatory studies. However it would be helpful if the guideline also covered earlier studies and the possible use of novel designs (i.e., adaptive or bayesian).	Not agreed. The scope of this guidance is focused on confirmatory trials aimed at supporting MAA.
Section 4.1.2, paragraph 1, line 2	It is not clear what is meant by ".. recent visualisation of the GIT ….".	Change to: '…. sufficiently documented by recent (within 12 months) visualisation of the gastrointestinal tract ….' Not agreed. The proper timepoint for visualisation could be different dependent on which phenotype of disease that is studied. Often a sigmoidocopy or colonoscopy is performed as part of the protocol of the study.
Section 4.1.2, paragraph 1, line 2	The need to document the extent of disease in this study design section needs to be clarified (i.e., if stratification is required then this should be stated directly). The extent of disease may be a prognostic factor for the risk of surgery but it is not a risk for severity at intake of a study.	Change to: 'The extent of Crohn's disease may be useful in clarifying whether the response is different in patients with disease in different locations, recognizing that the Montreal classification (2005) does not consider the four locations (ileal, colonic, ileocolonic, isolated upper disease) to be mutually exclusive. The site of the disease and associated complications must be recorded.' Partly agreed. Current wording does not indicate that pre-randomization stratification is necessary.
Section 4.1.2, paragraph 2, line 1	In order to avoid any confusion it needs to be made clear that the 'treatment under double-blind conditions should continue until the completion of the study period.' refers to the active treatment	Change to: 'Treatment under double-blind conditions should continue until the completion of the active treatment period in the absence of clinical deterioration or failure ….'

	period and not to a follow-up period.	Agreed. The text has been amended
Section 4.1.2, paragraph 2, line 3	The second sentence 'In all cases follow-up should continue until the planned end of the study.' needs clarification. What is meant by the 'end of study'? Is it for the individual patient or the whole study? There is little value in collecting follow-up data from patients who failed study treatment as they will have received alternative therapy.	Change to: 'In all cases patients should complete the pre-specified follow-up period for the study.' Agreed. The text has been amended
Section 4.1.3, paragraph 1, line 3	The approvability for a first-line indication should be based on the balance of both benefit and risk. As such it should also be possible for a new drug which has been demonstrated to be less effective than the current standard of care (steroids) but with an improved safety profile to be approved for a first-line indication.	Change to: 'In order to support a first line indication in the treatment of active Crohn's disease, it is necessary to demonstrate that the drug has either the same or an improved risk/benefit profile as the standard of care, which currently in the majority of cases includes glucocorticosteroids.' Agreed. The text has been amended.
Section 4.1.3, paragraph 2	Choice of comparator: Please clarify whether co-administration of experimental compound with a biologic, e.g. anti-TNF agent, is suggested with regard to add-on indication.	Not agreed. The current wording is considered sufficient. In the example of anti-TNF it would be more relevant with a head to head comparison to an approved anti-TNF if the trial concerns a new biologic treatment.
Section 4.1.3, paragraph 2	What about acceptable background medication if the proposed new medication is to be add-on? Should the types and doses of these be kept stable in the event that a "sparing" claim cannot form part of an indication?	The following text should be added: 'The type and dose of established therapy should be fixed.' Not agreed. As in clinical practice, there should be steroid tapering when the disease is under control.
Section 4.1.4, paragraph 1, line 5	The definition of the severity of disease should be clarified. Previous products approved have defined moderate to severe CD as a CDAI between 220 and 450. Patients with CDAI >450 are typically hospitalised and therefore would not be suitable for study.	Change to: 'CDAI scores of 150-219 define a mildly active disease, between 220-450 define a moderately *to severely* active disease and scores > 450 define severely active disease.' Not agreed. The CDAI scoring system is used and the definitions have been used in several trials and should not be changed. The scoring system refers to untreated patients.
Section 4.1.4, paragraph 2, line 1	The time to effect may depend on the mechanism of action so mandating the treatment duration to 8 weeks is not appropriate.	Change to: 'The proportion of patients achieving remission within the period of about eight weeks is, in most cases, an appropriate primary end-point to justify short-term treatment of active Crohn's disease. However, the mode of action of the investigated drug needs to be taken into consideration.' Partly agreed. If justified it is possible to propose a different time for endpoint,

		which can be discussed in a Scientific Advice.
Section 4.1.4, paragraph 2, line 1	Primary endpoints: Newer agents have used a measure of achieving response (CDAI decrease of at least 100 points) as a primary endpoint for the basis of approval. This should also be included under primary endpoints.	Insert: 'A measure of achieving response (CDAI decrease >100 points) is also an appropriate primary endpoint. Not agreed. Goal of treatment is remission, which is the preferred primary endpoint.
Section 4.1.4, 4th bullet point	If laboratory measures of inflammation are to be included in the list of secondary endpoints some statement on how they should be used should be included to ensure that they give useful information. The Montreal Working Party (2005) concluded that 'the use of these markers for diagnosis is not currently justified, given the limited sensitivity of available markers" (Satsangi J et al, Gut 2006; 55:749). Thus, the use of such measures of inflammation should be considered 'exploratory' until more information is available.	Change to: 'Laboratory measures of inflammation (exploratory endpoints)' Partly agree. Laboratory measures of inflammation are important to follow up the response to a given treatment. The current text is sufficient.
Section 4.1.4.	Secondary endpoints: Clarification on specific health-related improvements/Patient Reported Outcomes to be considered acceptable and how they might be incorporated into the SmPC would be welcomed. Furthermore it would be interesting to learn about the CHMP perspective on biomarker assessment/utilisation for Crohn's disease.	Results of secondary outcomes in general can be considered for section 5.1 of the SPC. Validated PRO and QoL instruments should be used and the Guideline recommends e.g. the IBDQ. Biomarker development is encouraged for CD but any specific recommendation in this respect is outside the scope of this Guideline.
Section 4.1.4, paragraph 1 (after bullet points)	Clarification is requested as to whether steroid dependent patients in a flare would still be considered steroid dependent?	Yes. Steroid dependency is defined in the Guideline.
Section 4.1.4, paragraph 5, line 1	Final analyses of data would be stratified by disease localization and activity. It should be clarified that stratification would not be required at randomisation.	Agree. Stratification for disese localisation is not needed pre-randomisation.
Section 4.1.5, line 1	For long half-life products, the CHMP may wish to comment on treatment to steady state, especially for assessment of safety.	Considered outside the scope of the guidance.
Section 4.1.5, line 2	It would be helpful to state how long the follow-up period should be, or at least state that 'appropriate follow-up' is required.	Partly agreed. The text has been amended.

Section 4.1.5, line 2	The rationale for the follow-up period to see if remission is maintained at the end of follow-up is unclear. Would a labelling claim be permitted if test treatment showed superiority for maintaining remission?	Induction of remission can be studied either in separate trials or in combination trials. For combination studies, statistically and clinically significant results are required for both phases of the trial, induction and maintenance.
Section 4.1.5, line 2	Requiring a follow-up period off therapy could significantly impact enrolment in trials combining induction and maintenance therapy. The need to assess the period off of therapy is presumably linked to whether the treatment is to be administered cyclically or continuously. This assessment would likely be conducted during Phase 2 investigations. It is unclear whether background therapy would need to be discontinued during follow-up period.	Background therapy should remain unchanged (apart from steroid tapering) The need for follow-up does not apply to combination trials. Clarified.
Section 4.2.1, line 1	Requirement for one month in remission for inclusion into the maintenance trials makes it difficult to enrol patients from the induction trials. Definition of the remission endpoint requires remission for 2 weeks and this should be used as an inclusion criterion for the maintenance trials. In that situation all the patients who achieved the remission in the induction study can be entered into the maintenance study.	Change to: ‘ Patients who are in the remission as defined by a CDAI of < 150 for at least 2 weeks may be included into the trial.’ It is not agreed that a change from 2 to 4 weeks would affect significantly recruitment.
Section 4.2.1, line 1	Excluding patients not in remission precludes the study of patients who may not have shown remission but are still a clinically important patient population, i.e. patients who had clinical response during treatment of active disease. This may also add a burden to enrolment.	Partly agreed. For combination trials, preferably only patients in remission should be entered into the maintenance phase of the trial.
Section 4.2.1, paragraph 1, line 10	This implies that for combined studies if superiority is only reached for one of the phases then the results of the trial would not support that phase/indication. If clinically and statistically significant results are seen in only one part of the combination study the results should be allowed to support an application for such an indication.	Change to: ‘For combined studies, in order to allow a claim for both induction treatment and maintenance treatment to be made it is required that statistically and clinically significant results are obtained for both phases of the trial.’ Not agreed. The proposed wording is considered appropriate.
Section 4.2.1.	It should be clarified whether patients with study-induced	For combination studies, only patients that have participated in the first phase of

	remission would be studied with patients who are in remission but did not participate in a study (i.e. patients who are already in remission).	the trial should continue into phase II. There is no need for further clarification.
Section 4.2.3	Clarification is requested as to whether biologics would be classified as immunosuppressive therapies under these guidelines.	Biologics are not classified as immunosuppressants but in certain circumstances an active comparator with a biologic may be appropriate.
Section 4.2.3	The possibility of an add-on indication to established therapy is not discussed. If a study of standard of care versus standard of care plus study drug was performed is an add-on indication acceptable?	Yes. This is clear from the Guideline
Section 4.3.	Clarification is requested as to whether fistulizing Crohn's subjects could be evaluated as a substudy of a larger Crohn's study (e.g. induction and maintenance).	If prespecified, studies of fistulising disease may be evaluated as a substudy of a larger Crohn study if the substudy is of general good quality e.g. regarding endpoints and number of patients.
Section 4.3.	Please clarify whether co-administration of experimental compound with an anti-TNF agent is suggested with regard to add-on indication.	That is highly dependent of what kind of drug is studied.
Section 4.3.	Please clarify whether co-administration of experimental compound with an anti-TNF agent is suggested with regard to add-on indication.	That is highly dependent of what kind of drug is studied. In general, it would be more relevant with a head to head comparison to an approved anti-TNF if the trial concerns a new biologic treatment.
Section 4.3.	Clarification is requested regarding the evaluation of add-on therapy with regard to the delineation of the add-on versus refractory population, i.e. these populations are not necessarily mutually exclusive.	It is acknowledged that these populations may not be mutually exclusive but the final study design will depend on type of drug studied.
Section 4.3.	Clarification is requested on the evaluation of maintenance on treatment with respect to recommended duration of this study and timepoint for assessing closure of fistulas.	For maintenance treatment 12 months study duration is appropriate.
Section 4.3.	Regarding follow-up without treatment, it should be noted that withdrawal of therapy in fistulizing Crohn's disease patients may not be appropriate with respect to the pharmacokinetic and pharmacodynamic profile of the investigational product.	Not agreed. It is considered important to evaluate if a treatment effect is sustained.
Section 4.3, line 8	Ultrasound is the best method to detecting perianal fistulae and MRI is best for detecting abdominal fistulae.	Change to: '…using imaging techniques. Ultrasound and MRI are the recommended techniques to detect perianal fistulae and abdominal fistulae, respectively. These techniques can be used to demonstrate internal as well as

		external healing of fistulas. Reading ultrasound/MRI images should be blinded and preferably done centrally. Clinical assessment of drainage……' Not agreed. MRI is currently the recommended technique to demonstrate fistula healing. To conclude that ultrasound is the best method is not supported, although there are a considerable amount of data describing ultrasound. However, ultrasound is investigator dependent making this method less suitable for multicenter studies, Moreover, anal ultrasound may particularly painful in patient with complicated perianal fistula disease.
Section 5, paragraph 1, line 11	Nutrition therapy is not considered to be a good comparator. A recent review (Zachos M et al, Cochrane database Syst Rev 2007: (1):CD000542) of CD studies has shown that steroids were better at inducing remission.	Delete '… but in addition, nutrition therapy can be considered for comparison.' Not agreed. Nutritional therapy is used by many pediatricians and thus can be considered for comparison.
Section 5, paragraph 1, line 15	Clarification is requested on the PCDAI severity strata.	Change to: '….where scores < 10 reflects inactive disease 10-30 (inclusive) mild disease and scores >30 moderate to severe disease.' Agreed. The text has been changed.
Section 5, paragraph 1, line 17	Several studies have used a decrease in PCDAI of 15 over 12 months as clinically meaningful to define clinical response.	Agreed. The text has been changed.
Section 5, paragraph 1, line 20	Available literature does not suggest a compelling rationale for DEXA measurement of body composition in paediatric CD to recommend its routine use in clinical trials.	Delete: 'Use of dual-energy X-ray absorptiometry (DEXA) is recommended to evaluate body composition.' Not agreed. Body composition in children with CD is important.
Section 6.1, paragraph 2, line 1	The following revision is proposed for clarification regarding previously used agents.	Change to: 'Concomitant use of immunosuppressants in add-on studies may increase the risk for serious adverse events. ~~and~~ It is important to document the use of these agents in trials with new immunological treatments.' Agreed. The text has been changed.
COMMENTS FROM ECCO- European Crohn's and Colitis Organization/ECCO Scientific Committee		

SPECIFIC COMMENTS ON TEXT		
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
P: page, p: para; L: line P3, p2, L2	Grammar	Change comma to full stop after '…state.' Agreed. The text has been changed.
P3, p2, L3	The Vienna classification has been modified in specific ways	Add (after fistulising disease) 'modified by the presence of upper gastrointestinal or perianal disease.' Agreed. The text has been changed.
P3, p4, L3	This high prevalence of surgery only applies to those with ileal disease, not Crohn's in general	Change to '…more than 70% patients with ileal disease will require..' Agreed. The text has been changed.
P3/8 P3 L 5	Pain my be caused by other factors as well	……..serosal inflammation or abscess formation. Agreed. The text has been changed.
P3/8 P4 L1	5-ASA are also recommended for colonic disease	Medical therapy includes 5-ASA for colonic disease , corticosteroids Agreed. The text has been changed.
P4, p3.1, L15	Refractory Crohn's also includes refractoriness to anti-TNF therapy	Add (after last sentence on aza/MP) 'Patients are refractory to anti-TNF therapy if they make no initial response to two appropriate doses of anti-TNF therapy (primary non-responders), or subsequently lose response either to scheduled or episodic re-treatment (secondary non-responders).' Partly agreed. A line concerning primary non-responders is added.
P4/8 p 3.1 L2		Steroids (prednisone, prednisolone…) Agreed. The text has been changed.
P 4/8 p3.1 L3	Although common, elevation of CRP or ESR is not mandatory for disease activity, nor specific	…symptoms, possibly with evidence….. Agreed. The sentence has been reworded.

P4, p4.1.1, L4	Because remission is defined as a CDAI <150 and response is increasingly defined as a decrease in CDAI ≥100 points, it would make sense to define disease activity in groups of 100 points (mild = 150-250, moderate 250-450, severe >450) at least until a sensitive, responsive and validated index superior to the CDAI is developed [Irvine EJ. Assessing outcomes in clinical trials. In: Satsangi J, Sutherland LR, Eds. Inflammatory bowel diseases. Churchill Livingstone, London 2003, pp 319-33.]. This means that entry to a trial of active Crohn's disease should be a CDAI >250. The threshold of 220 was set in the past when response defined as a decrease in 70 points was considered acceptable. This is an inconsistency that needs to be resolved. The European Crohn's and Colitis Organisation originally proposed such a change, but reverted to custom as described here on the advice of reviewers. This is not just about tidying up numbers. The lower the CDAI at entry the higher the placebo response, which can disguise the effect of an effective treatment.	Delete the three lines after '..treatment' (L5), and replace by 'if response is defined as a decrease in CDAI ≥100 points (section 4.1.3), entry to a trial of active Crohn's disease should be set at a threshold CDAI of 250.' Add CRP Comment MT. It is agreed that a higher CDAI score at inclusion would probably decrease the placebo response. However, it is considered difficult to get consensus to a higher, lower limit of CDAI score at inclusion. Not agreed. The definition used in the past should be used. It is acknowledged that there is an inconsistency and that some patients will be responders (if in remission) despite a reduction of only 70 points, but this inconsistency is not considered crucial for evaluating results of clinical trials. It is not agreed to add CRP. While CRP may be useful as a follow-up tool and for predicting response, it is not appropriate for selecting patients for treatment/inclusion into trials.
P4, p4.1.1, L7	Previous studies have included a heterogeneous population of patients with active disease and, as a result, have often been under-powered to determine if therapy is of specific value in disease types or location. It has consequently been unclear (for example) whether treatment is of greater value for patients with colonic as opposed to small bowel disease. By powering the study for precise groups of patients, the chance of meeting endpoints that matter to patients (such as reduction in surgery) or using a relevant surrogate marker (such as mucosal healing in colonic disease) is increased. For instance, the high prevalence of surgery in patients with ileal disease presents an opportunity for using reduction in surgery as an endpoint in a maintenance study of patients with ileal disease, while an induction study that focuses on patients with active Crohn's colitis can use colonoscopic mucosal healing as a relevant surrogate marker. This overcomes some of the limitations of using disease activity indices as a marker of efficacy and would advance clinical practice.	Add after the last sentence 'Consideration should be given to reducing heterogeneity of disease location and behaviour in the patient population, so that the study has sufficient power to evaluate endpoints that matter to patients (such as reduction in surgery for ileal disease) or use a relevant surrogate marker (such as mucosal healing in colonic disease) in addition to evaluating response through activity indices.' Partly agreed, a sentence has been added.
P4/8	Care must be taken to avoid inclusion of patients with infectious	Add at the end of paragraph

P4.1.1 L 7	diarrhoea.	Agreed.
P5, p4.1.3, L5	Grammar	Move comma from after 'Unless' to after 'superiority' Agreed
P 5 P4.1.3 L4	In different disease forms first line therapy may differ. For example, first line therapy for fistulas may include antibiotics, immunosuppressive agents or anti- TNF drugs.	After glucocorticoids add: first line therapy for fistulas may include antibiotics, immunosuppressive agents or anti- TNF drugs. Fistulas is covered in a separate sub-section
P5, p4.1.4, L7	Remission is not defined by a reduction in CDAI, but by a CDAI value itself	Change the words 'reduction in' to 'a' Agreed.
P5, p4.1.4, L9	See comment on p4.1.1 above	Add after the last sentence 'The anomaly of defining remission as a CDAI <150 and response as a decrease in CDAI ≥100 points is recognised. This influences the threshold of CDAI for trial entry (section 4.1.1). This is acknowledged, see previous comment on CDAI at entry
P5, p4.1.4, endpoints	Appropriate secondary endpoints should include endpoints that matter to patients: Proportion in steroid-free remission Reduction in hospital admission or duration of hospital stay Reduction in surgical procedures The use of individual items from the CDAI has not been validated	Add to the appropriate secondary endpoints • Proportion in steroid-free remission • Reduction in hospital admission or duration of hospital stay • Reduction in surgical procedures Partly agreed. The list has been amended.
P6, p4.1.4, L5	Predictors of response or failure may include factors other than symptoms and clinical phenotype.	Add (after '…and failure.'): 'Other measures to identify predictors of response or failure to biological therapy, such as genotype, biochemical markers of inflammation, or trough drug concentration, should be considered.' Partly agreed. The text has been changed.
P6, p4.1.5, L1-2	Steroid-free remission is what matters and is not the same as 'remission defined by a CDAI <150'. To combine the two increases heterogeneity	Add (after '…into the trials.'): 'Patients in steroid-free remission should be distinguished from those in remission defined by a CDAI <150 whilst continuing steroids. Maintaining steroid-free remission should be the goal of therapy.' Agreed. The text has been amended.

P6, p4.1.5, L3	The statement as it stands suggests that all active treatment studies should be 'stand alone' and not linked into randomised induction and then re-randomised maintenance, or randomised induction and continued maintenance. Is this what EMEA intend?	Add (after '.follow up'): 'unless the induction study is linked to a re-randomised or continued maintenance therapy study.' Agreed. The text has been amended.
P6, p4.2.1, L3	Have a care for the patients! Repeating colonoscopy or small bowel radiology so soon is unpleasant and exposes a patient to radiation which might otherwise be clinically unnecessary	Add 'relatively' before 'recent' and change 'within approximately 12 months' to 'within approximately 36 months' Partly agreed. Although unpleasant it is considered that having some kind of endoscopic investigation of the patients is important when studying new therapies, some of them with considerate risk of side effects. In some cases a sigmoidoscopy may be sufficient and probably will the capsule endoscopy and/or MRT of the small bowel soon replacing traditional radiology in the assessment of IBD. To have three years as a limit of a more objective assessment of the disease seems to be a long time. The timelimit has been changed to 18 months.
Treat	Refractory populations are also treated with anti-TNF agents, which can serve as an appropriate comparison. This pertains particularly to fistulising disease	Add: Anti TNF agent may also serve as an appropriate comparator in selected patient populations Agreed. Anti-TNF agents can be considered in sub-populations and this is reflected in the Guideline.
P6, p4.2.4, L1	See comment on steroid-free remission above	Add (after '..in whom..' and before 'remission'): 'steroid-free' Agreed. The text has been amended.
P6, p4.2.4, L4	Endpoints that matter to patients (in addition to no surgery and steroid-free remission) should be included as appropriate secondary endpoints: Reduction in hospital admission or duration of hospital stay Quality of life (as measured by validated indices such as IBDQ, EuroQol-5D, SF36) Time to relapse (where criteria for relapse are pre-defined)	Add: Appropriate secondary endpoints include • Reduction in hospital admission or duration of hospital stay • Quality of life (as measured by validated indices such as IBDQ, EuroQol-5D, SF36) • Time to relapse (where criteria for relapse are pre-defined) Partly agreed. The text has been amended.
P7, p5, L18	See comments on steroid-free remission above. This is particularly apposite for adolescents and children	Add (after '.. should be..' and before 'remission'): 'steroid-free' Agreed. The text has been changed
P8, p6.1, L6	Trough drug concentrations are probably more informative than measuring antibody formation and is of clinical relevance.	Add (after last sentence); Measurement of trough drug concentrations is appropriate

		Not agreed. Antibodies are more relevant.
P8, p6.2, L5	It's not only surgery, but also hospitalisation and time off work/normal activities that matter to patients in evaluating whether the risks of a treatment or intervention are justified	Add (after '..surgical intervention'): '.., hospitalisation, interventional procedures, time off work or normal activities..' Not agreed. This has nothing to do with safety.