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

London, 21 February 2008
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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON THE DEVELOPMENT OF NEW MEDICINAL PRODUCTS FOR THE TREATMENT OF ULCERATIVE COLITIS

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

Add name followed by link to individual received comment (upon publication by Web Services)

	Name of Organisation or individual	Country
1	EFPIA	
2	Schering-Plough	
3	Centocor BV	
4	Millenium	
5	ECCO	

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW

EFPIA: Overall, the document provides a useful start in the development of guidance for medicinal products for UC. However, there are a number of points of concern, particularly regarding the flexibility of the guidance to allow for different types of study design. See 'Key Comments' section and later sections.

Key comments include:

- Further clarification on the requirements for Phase III trials is requested. As currently written the guideline could infer that an extremely large clinical programme is required, which could provide a disincentive to develop products for the disease, despite the high unmet medical need. It is acknowledged that there are differences between subgroups of disease, but a more pragmatic approach with an increased level of flexibility is needed.
- The guidance does not currently allow for, or encourage, the use of innovative designs, even in Phase II exploratory studies. The use of, for instance, adaptive designs or randomised withdrawal should be discussed and encouraged, as should smaller, proof of mechanism type studies.
- Placebo controlled trials should be possible in mild to moderate UC if justified.

The draft guideline focuses on induction of remission and maintenance of remission. It is recommended that "induction of remission" is amended to "treatment of active UC/improving symptoms" to reflect that induction of remission is not the sole treatment goal.

ECCO: The document is generally well considered and good. Detailed comments and supporting statements as follows.

SPECIFIC COMMENTS ON TEXT

1 INTRODUCTION

Line no. + para no.	Comment and Rationale	Outcome
First paragraph, line 6	Pancolitis is the more accepted and used term rather than total colitis. The term pancolitis is used elsewhere in the document and should be used consistently throughout.	Replace "…and 20 % have total colitis" by "*…and 20% have pancolitis.*" Endorsed and amended
Second paragraph, line 2	Some of the available 5-ASA products are indicated for the treatment of active disease (i.e. treatment of acute exacerbations), which includes improvement and induction of remission, whereas others are used specifically for the induction of remission. As treatment of active disease is the more inclusive indication (i.e. not limited to induction of remission but also including improvement endpoints) it is proposed to consistently throughout the guideline use the term "treatment of active UC" rather than "induction of remission in UC".	Replace "These agents are effective at inducing remission in UC and in maintaining remission in UC." by *"These agents are effective in treatment of active UC (by improving clinical symptoms or inducing remission) and in maintaining remission in UC."* Unchanged. The relevant treatment goal is induction of remission as safe and efficient alternatives exists for patients

		failing to achieve remission on medical treatment
Second paragraph, line 4	In underdeveloped countries steroids may de facto be considered to be a cheap alternative to other treatments for maintenance therapy. Therefore, the statement should be more qualified by adding the safety aspect.	Replace **"**Remission, however, cannot be maintained with steroids…" by "*Remission, however, cannot be safely maintained with steroids"* Unchanged. Remission cannot be maintained with steroids
Second paragraph, line 4	Just mentioning Azathioprine or 6-MP is considered too specific as other cytotoxic drugs are principally available.	Replace **"**Azathioprine (AZA) or 6-mercaptopurine (6-MP) have been employed…." by "*Cytotoxic drugs, such as Azathioprine (AZA) or 6-mercaptopurine (6-MP) have been employed…."* Unchanged. The use of AZA/6-MP is well established and reasonably well-documented which is not the case for other cytotoxic drugs
Second paragraph, line 6	*One anti-TNF∝ has been approved for the treatment of UC refractory to both corticosteroids and AZA/6-MP.* This is likely to change as additional anti-TNF agents are approved to treat UC. Therefore, it would be prudent to ground this statement in relation to time.	Replace with: '*In early 2006, the first anti-TNF∝ was approved for the treatment of UC refractory to both corticosteroids and AZA/6-MP'.* Endorsed and amended
Second paragraph, line 7	Methotrexate may also be used for the treatment of steroid dependent or refractory patients.	Add the following sentence after "AZA/6-MP" in line 7: *"Alternatively, Methotrexate may also be used for the treatment of steroid dependent or refractory patients".* Unchanged. Evidence for the efficacy of methotrexate is scarce.
Section 1 Paragraph 2	Though surgery is curative in the sense that the diseased tissue is removed, there is significant resultant morbidity and occasional mortality associated with colectomy.	Add comment on complications associated with colectomy Clarified.
Section Paragraph 2	The fact that mortality does not appear to be increased in UC in general puts the risk of colon cancer in context.	Add comment. Unchanged. Mortality in general is not increased.
P2 L8 and L12	The term 'acute severe colitis' is preferred to 'fulminant' colitis, because	The term 'fulminant' should be replaced here and throughout

	‘fulminant’ is ill-defined. It was coined in 1950 when it referred to a single attack going on to death within 1 year [Rice-Oxley JM, Truelove SC. Ulcerative colitis: course and prognosis. *Lancet* 1950; **i:**663-6], which no longer has relevance today. Severe colitis defined according to Truelove and Witts’ criteria are easy to apply in outpatients, determine a course of action (hospital admission for intensive treatment) and an outcome (only 70% respond to intensive therapy), as well as being used by The American College of Gastroenterology (ACG) [Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology Practice and Parameters committee. *Am J Gastroenterol* 2004; **99:** 1371-85]. Misuse of the term severe colitis has created confusion, most manifest in the Active Colitis Trials (ACT) of infliximab which used the term ‘severe’ colitis for outpatients with treatment-refractory active colitis [Rutgeerts P, *et al*. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **233:**2462-73]. This terminology was recommended by the European Crohn’s and Colitis Organisation (ECCO) [ECCO Consensus on the management of ulcerative colitis 2007. (in preparation)].	the document with ‘acute severe’ Endorsed and amended.
2 SCOPE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
3 CLINICAL TRIALS		
3.1 PATIENTS’ CHARACTERISTICS AND SELCTION OF PATIENTS		
Line no. + para no.	**Comment and Rationale**	**Outcome**

Section 3.1.1 first paragraph, lines 2- 4	Histological findings can be supportive in the diagnosis of UC but are not as specific as endoscopy or clinical criteria.	Amend to: *'The diagnosis of ulcerative colitis should be based on patient history (diarrhoea and rectal discharge of blood and/or pus) and endoscopic findings (continuous oedema, friability, granularity and ulcerations in colorectal mucosa). Histological findings (crypt distortion/abscess, ulceration) can be supportive diagnostic criteria'.* Unchanged. Diagnosis should be based on both clinical, endoscopic and histological findings.
Section 3.1.1, first paragraph, line 5	Add brackets behind "ulceration"	Amend to: *'(crypt distortion/abscess, ulceration)'.* Endorsed and amended
Section 3.1.1 first paragraph, lines 5-6	Current wording suggests that exclusion of malignancy should be a study related procedure. However, typically only sigmoidoscopy to assess severity of UC is done. Therefore, clarification is suggested.	Replace with: *'Infectious causes of colitis must be ruled out. Malignancy should be excluded but not necessarily assessed as a mandatory study related procedure. Medical history may be taken into account'.* Unchanged. The section is related to disease diagnosis not inclusion criteria.
Section 3.1.1 first paragraph, lines 6 - 9	Classification of extent of disease appears to be based on that given in the UK treatment guidelines (ref: Carter MJ et al (2004) Guidelines for the management of inflammatory bowel disease in adults; GUT, 53, pp1-16). It would be more appropriate to use the Montreal classification (ref: Satsangi J et al (2006) The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications; GUT, 55, pp749-753). This classification is considered to be more biologically relevant (e.g. with respect to response to topical therapy) and corresponds to the natural history of the disease.	Change to: *"Depending on the extent of disease, patients can be classified as having 1) ulcerative proctitis involving only the rectum, 2) left sided UC (distal UC) involving colorectum distal to the splenic flexure and 3) extensive UC (pancolitis) involving colorectum proximal to splenic flexure."* Endorsed and amended.
Section 3.1.1,first paragraph, line 15	*Depending on the disease activity, patients can be classified as being in remission or having mild, moderate, or severe disease activity, e.g. according to the criteria for Truelove and Witts.* In addition to the Truelove/Witts criteria, there are newer indices that use biochemical or molecular markers or endoscopic appearance of the colon to classify patients. These indices are also useful to classify patients in clinical trials.	Amend to: *'Depending on the disease activity, patients can be classified as being in remission or having mild, moderate, or severe disease activity according to one or more measures of disease severity, such as the criteria of Truelove and Witt's.* Partly endorsed and amended. Reference to specific indices has been deleted.

Section 3.1.1, third paragraph, line 2	Refractory disease: Guidance on the adequate dose and time period for the use of corticosteroids before a patient is defined as steroid refractory or dependent should be given (see D'Haens et al (2007) A review of activity indices and efficacy points for clinical trials of medical therapy in adults with ulcerative colitis, GASTOENTEROLOGY, 132, pp 763-786).	Add the following paragraph after *"…should be classified as being steroid dependent": 'A steroid-dependent state could be defined as partial or complete clinical response to treatment with prednisone 40–60 mg/day and relapse within 30 days after prednisone treatment was completed or relapse with attempted dose reduction of prednisone resulting in the use of prednisone at doses of ≤15–25 mg/day for at least 6 months. A steroid refractory state could be defined as no response to prednisone at doses of 40–60 mg/day within 30 days'.*" The definition is arbitrary and thereof no specific definition can be provided. The text has been clarified.
Section 3.1.1 third paragraph	Refractory disease: The definition of refractory disease should be modified since patients can show some improvement to treatment but still exhibit symptoms of active disease and thus are still considered to be refractory.	Change 1st sentence to:" *Patients who continue to have active disease (defined according to activity index used) despite the use of corticosteroids in an adequate dose and for an adequate time period are defined as being steroid refractory."* Change 3rd sentence to: "*Patients are refractory to azathioprine/6-mercaptopurine if they continue to have active disease despite 3 to 6 months of treatment with a sufficient dose."* Endorsed and amended
Section 3.1.2, first paragraph, line 1	Replace "definite ulcerative colitis" by "confirmed ulcerative colitis"; definite appears to be a too strong term	Replace with: *'Only patients having confirmed ulcerative colitis should be included in trials'* Endorsed and amended
Section 3.1.2, first paragraph, lines 1-2	"Recent" definition of extent of the disease implies the need for colonoscopy at baseline screening; however, only sigmoidoscopy is typically performed at this stage. Therefore, determination of extent of disease should be based on historic data.	Replace with: '*Extent as well as severity of the disease should be defined based on medical history or recent clinical and endoscopic evaluation, respectively'.* Unchanged. The extent of disease is one of the major determinants of management and response to treatment and therefore has to be documented at entry. The current wording does not imply that colonoscopy is necessary.
Section 3.1.2; first	See earlier: As treatment of active disease is the more inclusive	Replace "The study population should reflect the specific

paragraph, line 4-5	indication (i.e. not limited to induction of remission but also including improvement endpoints) it is proposed to consistently throughout the guideline use the term "treatment of active UC" rather than "induction of remission in UC".	aim of the treatment (induction of remission or maintenance of remission), …" by "*The study population should reflect the specific aim of the treatment (treatment of active UC or maintenance of remission), …*" Unchanged. The relevant treatment goal is induction of remission.
Section 3.1.2; second paragraph, line 1	Diverticular disease associated colitis should be added to the list of exclusion criteria	Endorsed and amended
3.1.1	Definitions and diagnostic criteria: Depending on the extent of disease, patients can be classified as having 1) distal disease involving only the rectum (proctitis) or the rectum and the sigmoid colon (proctosigmoiditis), 2) left-sided disease (extending from the rectum to the splenic flexure, 3) extensive disease (extending from the rectum to the hepatic flexure) and 4) pancolitis (involving the entire large intestine).	According to ICD criteria only 3 levels are used (K51.0=Extensive/total colitis, K51.3 Left sided colitis, and K51.2 proctitis) However a four step scale is often applied as well The 3 level Montreal classification as now recommended but that classification closely matches the ICD criteria.
3.1.1	Depending on the disease activity, patients can be classified as being in remission or having mild, moderate or severe active disease, e.g. according to the criteria of Truelove and Witts.	Remission is not strictly defined by Truelove and Witts. Endorsed and amended. The mentioning of specific criteria has been deleted.
3.1.2	In general, it would be relevant to study either distal disease (proctitis or proctosigmoiditis) or disease involving more proximal sections of the large bowel (left-sided, extensive and pancolitis combined), as the former groups are mainly treated with rectal topical treatment whereas the latter requires systemic treatment with or without topical treatment	Agree that topical therapies should be tested on distal colitis, but disagree that distal colitis should be excluded from systemic treatment trials. Partly endorsed and amended. Distal colitis has been replaced by proctitis. Proctitis in general requires topical treatment only.
Section 3.1.1 Paragraph 1	There are numerous criteria used to assess disease activity and several have been employed in registration trials. Mentioning only one specific set of criteria (Truelove and Witts) implies that these are favored. Furthermore, in section 3.2.2, no preferred clinical activity index is mentioned.	Mention other disease activity indices or mention none. Add reference to section 3.2.2. Endorsed and amended.

<table>
<tr>
<td>Section 3.1.1</td>
<td><u>Definitions and diagnostic criteria – Refractory disease</u>
The Guideline states,”Patients exhibiting no improvement (defined according to activity index used) despite the use of corticosteroids in an adequate dose and for an adequate time period are defined as being steroid refractory. …. Patients are refractory to azathioprine/6-mercaptopurine if they do not respond to a sufficient dose within 3 to 6 months of treatment start.” Not infrequently, patients may experience some improvement on treatment, but insufficient improvement to be evaluated as being in remission against prespecified criteria. Therefore, adherence to the draft Guideline would create three groups of patients: those who are refractory (no response to treatment); those who enter remission (satisfactory response to treatment); and those who respond but do not enter remission, as defined (unsatisfactory response to treatment). This is problematic for the development of new therapies since, in clinical terms, the induction of remission should be a binary evaluation leading to only two populations of patients (those who have, or have not, entered remission). This is the clearly intended predicate of the statement, later in the Guideline, that “For steroid refractory patients, the primary endpoint should be induction of remission”. Therefore, we believe that patients who respond to some extent, but who do not enter remission, should be considered to be refractory to treatment.</td>
<td>Accordingly, we recommend that the guideline should be rephrased as follows: “Patients who do not enter remission (defined by prespecified criteria using an appropriate activity index) despite the use of corticosteroids in an adequate dose and for an adequate time period are defined as being steroid refractory. …”

Endorsed and amended</td>
</tr>
<tr>
<td>P1 L5.</td>
<td>Close bracket is missing</td>
<td>Corrected</td>
</tr>
<tr>
<td>P1 L6</td>
<td>Diseases extent is best classified according to the Montreal classification and supported by ECCO. This divides extent into proctitis, left-sided and extensive disease [Silverberg MS, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a working party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005;19 suppl A:5A-36A].

Montreal classification of UC according to disease extent
<table>
<tr><th></th><th>Extent</th><th>Description</th></tr>
<tr><td>E1</td><td>Ulcerative proctitis</td><td>UC limited to the rectum (ie proximal extent is distal to the rectosigmoid junction)</td></tr>
<tr><td>E2</td><td>Left-sided UC</td><td>Involvement limited to the colon and rectum distal to the splenic flexure (includes distal UC)</td></tr>
</table>
</td>
<td>This terminology should apply to the whole document.

Endorsed and amended.</td>
</tr>
</table>

	E3 Extensive UC — Involvement proximal to the splenic flexure (includes pancolitis)	
L10	The risk of proximal extension of distal disease is not 'approximately 50%', but up to 30%. In a population-based study of 1161 patients with ulcerative colitis, 48% had proctitis or distal disease, 32% left-sided, 18% total colitis and 2% undefined at presentation [Langholz E, Munkholm P, Davidsen M, Binder V. Course of ulcerative colitis: analysis of changes in disease activity over years. *Gastroenterology* 1994, **107:** 3-11]. Subsequent proximal extension has conventionally been estimated at around 15%, but appears to be higher. In a retrospective study of 145 patients with distal colitis at presentation, disease extension proximal to the sigmoid was recorded in 36% at a median of 6 years, becoming extensive in 29% [Ayres RC, Gillen CD, Walmsley RS, Allan RN. Progression of ulcerative proctosigmoiditis: incidence and factors influencing progression. *Eur J Gastroenterol & Hepatol* 1996; **8:** 555-8]. Using actuarial analysis, disease extension was predicted for 16% (CI, 11-24%) at 5 years and 31% (CI, 23-40%) 10 years after diagnosis. A similar proportion (27%) had disease extension in a larger study of 273 patients with distal UC, but only a minority extended beyond the splenic flexure (4% and 10% at 5 and 10 years respectively) [Meucci G, Vecchi M, Astegiano M, et al. The natural history of ulcerative proctitis: a multicenter, retrospective study. *Am J Gastroenterol* 2000; **95:**469-73]. In contrast, in 399 patients with UC, the extent regressed in 22%, with 30% having a normal colonoscopy 14 months after diagnosis [Moum B, Ekbom A, Vatn MH, Elgjo K. Change in the extent of colonoscopic and histological involvement in ulcerative colitis over time. *Am J Gastrenterol* 1999; **94:**1564-9]. .	Endorsed and amended
P2 L1	'acute severe colitis', not 'fulminant'	Endorsed and amended.
3.1.1 Refractory disease	The term 'steroid refractory' should be defined. The definition agreed by ECCO is 'Patients who have active colitis despite prednisolone up to 0.75mg/Kg/day over a period of 4 weeks'. This was agreed by 45/58 European IBD experts (Sep 06), is consistent with the definition for steroid-refractory Crohn's disease [ECCO. European evidence based	The term 'steroid refractory' should be defined The definition is arbitrary and thereof no specific definition can be provided. The text has been clarified.

	consensus on the diagnosis and management of Crohn's disease. *Gut* 2006;**55 Suppl 1:**i1-58] and others [D'Haens G, Sandborn WJ, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology* 2007;**132:**763-86].	
3.1.1 Steroid dependency	The term should be defined. The definition agreed by ECCO is 'Patients who are either i) unable to reduce steroids below the equivalent of prednisolone 10mg/d (or budesonide below 3mg/d) within 3 months of starting steroids, without recurrent active disease, or ii) who have a relapse within 3 months of stopping steroids. This was agreed by 52/58 European IBD experts, is consistent with the definition for steroid-dependent Crohn's disease, although an alternative definition of relapse within 30 days of completing a course of steroids, or steroids at a dose of 15-25mg/day for at least 6 months has been proposed [D'Haens & Sandborn 2007]. The ECCO definition of steroid-dependence requires that the total duration of steroids does not exceed 3 months before a threshold equivalent to prednisolone 10mg/d is reached. Patients are still considered steroid-dependent if they relapse within 3 months of stopping steroids. Although these limits are arbitrary, they serve as guidance for clinical practice and may be used for uniformity in clinical trials.	The definition is arbitrary and thereof no specific definition can be provided. The text has been clarified.
	Remission is defined as complete resolution of symptoms and endoscopic mucosal healing. Combining clinical and endoscopic assessment is appropriate for clinical trials [Rutgeerts P, et al. Mucosal healing in inflammatory bowel disease: impossible ideal or therapeutic target? *Gut* 2007;**56:**453-5], but remission rates vary by as much as two-fold depending on the definition of remission used in the trial [Travis SPL, Dinesen L. Remission in trials of ulcerative colitis – what does it mean? *Practical Gastroenterol* 2006; **30:**17-20].	Add new paragraph on '*Remission'* Unchanged. Definition of remission will depend on the index used for assessing disease activity see paragraph *3.2.2*
3.1.2 Inclusion criteria/Exclusion	Add after second sentence 'For trials of active colitis, endoscopic a histological evidence of disease activity should be established, since	Partly endorsed and amended.

criteria P1 L2	absence of histological evidence of inflammation at trial entry excludes diagnosis of active colitis'.	
P1 L7	Amend disease distribution terms to conform with 3.1.1 (above).	Endorsed and amended
P1 L14	Precisely: see above definitions.	See above
P1 end	Additional sentence 'For patients entering a trial of maintenance thera evidence of a relapse within the preceding 12 months is appropriate increase the likelihood of demonstrating benefit from the maintenance agen	Partly endorsed and amended
P2 L6	Exclusion of infections should be mandatory and phrased stronger th "may". It should also precede any treatment not only in cases immunosuppressive agents. This should include testing for parasites, st culture and presence of C. Diff toxin. In patients treated with previc immunosuppressive therapy exclusion of CMV infection should be perform as well.	Partly endorsed and amended
3.1.3 Baseline characterist P1 L1	Suggest Body Mass Index (BMI) in addition to weight, also document smoking status P1 end: Recommend that consent is obtained and samples taken at baseline for storage for DNA analysis and serology A major opportunity was missed in the PRECiSE, CHARM and other trials of biotherapy in this regard.	Addition of BMI and smoking status endorsed and amended Second comment outside the scope of a regulatory Guideline

3.2 METHODS TO ASSESS EFFICACY		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Section 3.2.2., second paragraph,	The induction of remission is the ultimate but not necessarily the only goal of treatment of active disease. Primary endpoints may include induction of remission but may not necessarily be limited to it. Improvement of symptoms related endpoints may also be a valid primary endpoint.	Replace "The therapeutic goal is to induce remission" by '*The therapeutic goals include improvement of symptoms or induction of remission'.* Unchanged. The relevant treatment goal is induction of remission.
Section 3.2.2, second	• *Treatment of active disease:. For studies of add-on in patients on steroids, a scheduled steroid taper should be considered mandatory.*	Replace with*: 'For studies of add-on in patients on steroids, a scheduled steroid taper should be considered mandatory.*

paragraph, lines 5-6	While a steroid taper is required, it is not likely that the steroid taper can be completed in time to assess efficacy after 4-8 weeks of therapy. More time is needed to taper steroids and assess the impact of this activity. Furthemore,, this sentence suggests that a remission definition necessarily includes "tapered off steroids". This might not be clinically reasonable as clinical remission can be achieved well before steroid taper is complete. If this is the intended meaning, then this is inconsistent with wording in paragraph 3 ,Maintenance of remission', in that steroids are allowed at entry for the maintenance of remission trials while at the same time saying that "*Patients included should be in clinical and endoscopic remission*"	*The trial design must grant adequate time to taper steroids and assess the impact'.* First comment endorsed and amended Steroid tapering refers to add-on studies, therefore not inconsistent. For refractory patients steroids are allowed at baseline at entry into maintenance trials
Section 3.2.2., second paragraph, lines 9-10	The induction of remission is the ultimate but not necessarily the only goal of treatment of active disease. Primary endpoints may include induction of remission but may not necessarily be limited to it. Improvement of symptoms related endpoints may also be a valid primary endpoint.	Replace "For steroid refractory patients, the primary endpoint should be induction of remission." by "*For steroid refractory patients, the primary endpoints should be improvement of symptoms or induction of remission."* Unchanged. The relevant treatment goal is induction of remission, including steroid refractory patients
Section 3.2.2, third paragraph, line 1	• *Maintenance of remission:.Patients included should be in clinical and endoscopic remission at entry.* This statement prevents subjects from achieving remission in the maintenance phase given that they did not achieve remission in the induction phase. This is contrary to data from other clinical trials in the UC population (e.g. infliximab) where remission was achieved late in the trial.	Replace with*: 'It is recommended that patients should be in clinical and endoscopic remission at entry. However, patients who are improving in the induction phase may be candidates for the continuing therapy in the maintenance phase'.* Unchanged. The primary endpoint of maintenance of remission implies that patients are in remission baseline. This is also in accordance with clinical practice, i.e. only when remission has been achieved is maintenance treatment introduced. If patients with response are allowed to enter the maintenance phase the primary endpoint will still have to be based on patients in remission.
Section 3.2.2, third paragraph, lines 4-6	• *Maintenance of remission:. For patients on steroids at entry, steroids must be discontinued within the study period according to a pre-specified schedule and not reinstituted for at least 6 months.*	Clarified

	This statement appears to require that all subjects on steroids at entry must have steroids discontinued. This differs from the approaches taken in the Treatment of active disease section where inability to discontinue steroid treatment can be a co-primary endpoint and steroid refractory patients may exist. The Maintenance of remission section should also acknowledge these two groups of patients.	
Section 3.2.2 fourth paragraph, line 2	Histology can also be used as a secondary endpoint when assessing the clinical efficacy of a treatment.	Amend to: "*Other secondary endpoints could include histology, changes in stool frequency….*" Endorsed and amended
Section 3.2.2 fourth paragraph, lines 5-6	It is stated: "*For steroid dependent disease reduction of steroid dose is an important secondary parameter*." It should be clarified whether reference is made to steroid dependence or steroid refractoriness. Indeed, this is inconsistent with the previous section where it is stated that "*For steroid dependent patients, remission and ability to discontinue steroid treatment should be co-primary endpoints*».	Endorsed and amended
3.2.2 1st paragraph: Primary efficacy endpoint	Since endoscopic appearance correlates to signs and symptoms and to biochemical measures of inflammatory activity it is not compulsory to include endoscopy in the primary efficacy scores (potential confounding of endoscopy, time lag, observer variation).	The correlation of signs and symptoms with endoscopic appearance is not widely accepted by gastroenterologists. There is still keen interest to correlate mucosal healing with clinical symptoms. Unchanged. A correlation between clinical activity and endoscopic appearance has been documented.
3.2.2. 1st bullet: Treatment of Active Disease	The therapeutic goal is to induce remission.	Remission is the desired therapeutic goal, and can be achieved in 1 of 3 patients with new therapeutics like infliximab. However, 2 in 3 patients achieve a meaningful clinical response after infliximab treatment. Thus achievement of remission as the primary goal does not take into account clinical reality and the need of patients to have the possibility to at least lower disease activity even if they

		cannot achieve remission. In addition, remission as primary endpoint will require clinical trials with large number of patients, thus making clinical development for new drugs very costly in a patient population with currently limited options. Unchanged. The relevant treatment goal is induction of remission.
Section 3.2.2	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 ulcerative colitis, clinical response is a clinically relevant endpoint for the assessment of therapeutic efficacy and clinical response provides information on a substantially greater proportion of patients treated with infliximab as an example. In the ACT studies, 66% of infliximab-treated subjects were induced into clinical response at Week 8 (placebo - 33%) . In contrast, in the same studies ~ 33% of infliximab-treated subjects were induced into clinical remission at Week 8 (placebo ~ 10%). Consequently, the remission endpoint provides information on the treatment outcome in one third of patients whereas the response endpoint provides information on the treatment outcome in two thirds of patients. Furthermore, the ACT studies showed that 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 ulcerative colitis. Furthermore, physicians continue treat patients who have responded , but are not attained remission. Therefore, because the response endpoint provides clinically relevant	Provide rationale for choice of primary endpoint other than ideal treatment outcome. Primary endpoint should be clinically relevant and reflect efficacy profile in substantial proportion of patients. An endpoint that reflects clinically relevant efficacy in two thirds of the patient population should be preferred over an endpoint that reflects efficacy in only a third of the population. Unchanged. The relevant treatment goal is induction of remission.

	information on treatment outcome in approximately twice as many patients relative to the remission endpoint it is the most appropriate endpoint for use in trials of anti-TNF therapies in UC trials.	
Section 3.2.2	Efficacy criteria in main therapeutic studies – Primary efficacy studies – Treatment of active disease The Guideline states, *"Colectomy rate at 12 months is the relevant parameter in studies of patients with active, severe disease failing usual medical therapy."* We believe that colectomy rate at 12 months is not an appropriate endpoint to evaluate induction of remission. First, the observation period of 12 months is too long for an evaluation of induction of remission and would, in fact, evaluate the therapy's effectiveness in inducing and maintaining remission. As the Guideline states elsewhere (Section 3.3 – Strategy and Design of Clinical Trials – Aim of treatment), *"It cannot be assumed that a medicinal product that is effective in inducing remission is also effective in preventing relapses once remission is achieved. Therefore, both* (sic) *indications will have to be studied separately in Phase III trials."* Second, the proposal in the Guideline makes three assumptions, some or all of which may be fallacious in a given study: a) that patients who do not remit will proceed directly to colectomy, rather than another medical intervention; b) that patients will not enter remission, then relapse before 12 months; c) that patients who relapse will undergo colectomy forthwith, rather than treatment with another medical therapy. Each of these scenarios would invalidate colectomy rate as an endpoint for induction of remission in active disease. Moreover, recent data[1] indicate that European colectomy rates in patients recruited over short inclusion periods from populations outside tertiary care centres are much lower than may have been inferred from previous studies. These are important data that specifically call into question the basis for, and the practical utility of, the Guideline's recommendation to use colectomy rate as an endpoint in induction of remission studies. We believe that colectomy rate can be a useful endpoint, but that it should be used to evaluate maintenance of remission when the study protocol prespecifies that patients who relapse within the time period will proceed directly to colectomy. We recommend that the Guideline is modified accordingly.	Therefore, under the Guideline's own recommendations, the colectomy endpoint should be discussed in relation to maintenance of remission rather than induction of remission. Partly endorsed and clarified

[1] Hoie, O.; Wolters, F.L. and others. Low Colectomy Rates in Ulcerative Colitis in an Unselected European Cohort Followed for 10 Years. *Gastroenterology* (2007), **132**, 507-515.

Section 3.2.2	Efficacy criteria in main therapeutic studies – Primary efficacy studies – Maintenance of remission The Guideline states, *"Patients should be in clinical and endoscopic remission at entry"*. As a practical matter, complete epithelial healing usually does not occur until some time (several weeks to several months) after remission of clinical signs and symptoms. Therefore, under the provision of the Guideline, there may be an unnecessarily extended delay between clinical remission and the time when patients can be randomized to study treatments to maintain remission. If remission is induced with a drug that is not the investigational drug, there should be an appropriate wash-out period but, beyond that, it would be optimal to keep the interval between clinical remission and the commencement of maintenance treatment as short as possible. Further, the Guideline itself states that *"Since endoscopic appearance correlates to signs and symptoms … , it is not compulsory to include endoscopy in the primary efficacy scores"* [for induction of remission], thus there is already an acceptance elsewhere in the document that endoscopy is not a primary indicator of remission.	We recommend that there should be no requirement for endoscopic remission at study entry, but only a requirement for clinical remission with clinical evidence of epithelial healing (i.e., decrease in rectal bleeding, diarrhoea). Endorsed and amended
Section 3.2.2	Maintenance of remission The Guideline does not specify that patients selected for maintenance of remission studies should have remitted recently from active disease. Potentially, this allows the introduction of bias because, if patients have been in remission at enrollment for significantly different periods, there is likely to be inequality in their probability of relapse. A fraction of patients with quiescent disease may not relapse and would therefore be inappropriate for studies investigating efficacy in maintenance of remission.	We recommend that a statement should be included to the effect that patients should enter maintenance of remission studies directly after the remission of their active disease. Unchanged. With proper randomisation patients with different periods of remission should not be a problem as these will be equally distributed between the groups. That sensitivity could be increased by including patients with recent remission is now mentioned in the guideline, see paragraph 3.1.2
3.2.2	Efficacy criteria *Primary* P1 L3: Omit 'Generally'	
P1 L5	Add 'broadly' before 'correlates'	
	Treatment of active disease: Amend para 'The therapeutic goal is to indu steroid-free remission. The precise definition of remission depends on index used, but should represent normalisation of stool frequency, absence	Partly endorsed and clarified. For patients on steroids, the aim is steroid-free remission.

	blood in the stools and lack of urgency, confirmed by endosco Additionally, biochemical markers of inflammation such as CRP are l reliable in UC, a fact that further supports the use of endoscopy Data should be collected in a form that is clinically relevant patients…Colectomy rate at 12 months is the relevant parameter in studies patients with acute severe colitis failing usual medical therapy. …. Please note that if an 8 week limit is set, then treatments such as AZA would not be included. Hence a 12 week period should be permitted, but the label should reflect this.	A correlation between clinical activity and endoscopic appearance has been documented making the requirement for endoscopy confirmed remission unnecessary. This is also consistent with clinical practice. The comment regarding colectomy rate is endorsed and the text amended accordingly.
	Maintenance of remission Amend para '…..The primary efficacy parame should be the proportion of patients maintaining steroid-free remiss throughout the period. Clinical relapse should be distinguished from ac infectious disease, but need not be confirmed by endoscopy. Criteria relapse should be predetermined, according to the activity index us Preferably including rectal bleeding.	
	Secondary efficacy endpoints Add after first sentence 'For this reas independent symptom, endoscopy and quality of life indices are preferred composite indices that combine these measures. Independent indices are m readily validated and subscores are more likely to be relevant to clini practice than derivations from a composite index.'	
	P1 L3: add 'urgency' after 'disappearance of visible blood in faeces'	

3.3 STRATEGY AND DESIGN OF CLINICAL TRIALS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Section 3.3, first paragraph, line 1	As mentioned above, while induction of remission certainly is one important goal, improvement of symptoms may also be a valid aim of treatment of active disease.	Replace "The aim of pharmaceutical intervention in UC is to induce remission and to prevent relapses…" by *"'The aim of pharmaceutical intervention in UC is to improve or eliminate symptoms of disease and to prevent relapses…"* Unchanged. The relevant treatment goal is induction of remission.
Section 3.3, first	Where scientifically plausible (based on biological and pharmacological	Amend to: "*Therefore, both indications will need to be*

paragraph, line 4	reasons), the absolute requirement to study both induction of remission and maintenance of remission as separate Phase III studies should be removed. Study designs exist where it is possible to study both without compromising the main objectives of the trial. This approach should be encouraged since it allows for a more flexible and innovative approach in an area where there is a high unmet medical need. This approach is encouraged in the draft EMEA reflection paper on methodological issues in confirmatory clinical trials with flexible design and analysis plan (ref: EMEA/EWP/2459/02). It should also be clarified whether the sub-groups (for instance steroid dependent) can be studied in trials in the wider UC population, with the appropriate stratification.	*adequately studied in order to obtain approval and labelling in both indications. This can be accomplished in separate Phase III studies, or where appropriate, in combined studies that have been adequately designed. It is not a requirement however to study both indications in order to be able to seek registration for one indication."* Partly endorsed and amended
Section 3.3, first paragraph, line 5	*'Modified indications are possible for certain sub-groups of patients such as steroid refractory or steroid dependent patients'.* In addition, Section 3.2.2, Secondary efficacy endpoints, states, *For steroid dependent disease, reduction of steroid dose is an important secondary parameter*.' Please clarify if these sentences are intended to mean that an indication of "reducing or eliminating steroid use in steroid-dependent disease" can be based on a secondary efficacy endpoint.	Endorsed and clarified
Section 3.3 second paragraph, line 3	It is stated: "*For locally acting products, distribution studies are necessary, e.g. by scintigraphy*". It is unclear what the justification is for use of scintigraphy as a method for studying the distribution of locally active products. Suggest that this example is removed from the document.	Replace with: *" For locally-acting products, distribution studies are necessary".* Endorsed and amended
Section 3.3.1, first paragraph, lines 3-4	Although placebo controlled, parallel group, double blind trials are appropriate in many situation, the use of innovative designs for exploratory studies can also be appropriate (for instance randomised withdrawal) and should be encouraged. The requirements for Phase II studies should allow for this.	Amend to: '*Whilst the design of Phase II trials in UC as parallel-group, double blind, placebo-controlled is often appropriate, the use of innovative designs (e.g. randomised withdrawals) where appropriate is encouraged.'* Endorsed and amended
Section 3.3.1, second paragraph, lines 1-3	There could be study designs that allow for the study of both objectives (dose-response in induction of remission and prevention of relapse) in one study therefore separate studies are not always required.	Amend to:' *Different doses may be needed for induction of remission compared with prevention of relapse and this may*

		be accomplished in separate studies or as one study'. Unchanged. The sentence does not exclude the possibility of exploring both induction and maintenance regimens within the same study.
Section 3.3.1, third paragraph, line 2	Biomarkers should be required to be validated in UC specifically. This can be achieved as a sub-study of the clinical trial.	Partly endorsed and clarified.
Section 3.3.2, first paragraph	Further clarification on the requirements for Phase III trials is requested. As currently written the guideline implies that two separate Phase III trials are required for each indication (induction of remission and maintenance of remission) in each sub-group of disease (for example proctitis, left sided UC and extensive UC) in each severity of disease (mild-moderate-severe). In addition the current wording could also be interpreted to mean that sub-groups of disease (e.g. steroid dependent and steroid refractory) should be studied in additional large clinical studies. Hence the current wording could infer that an extremely large clinical programme is required, which could provide a disincentive to develop products for the disease despite the high unmet medical need. It is acknowledged that there are differences between subgroups, but a more pragmatic approach with an increased level of flexibility is needed.	Unchanged. The main sub-groups of patients, i.e. patients with active disease versus patients in remission need separate studies as well as patients with acute, severe (fulminant) colitis. Otherwise, the study population should match the intended use of the new product and it is obvious that one study including all different categories of patients with UC is not feasible. One drug does normally not suit all.
Section 3.3.2. second paragraph, line 1	As mentioned above, while induction of remission certainly is one important indication, treatment of acute exacerbations (i.e. improvement of symptoms) is also a valid indication.	Replace "With regards to the indications, induction of remission and prevention of relapse…" by "*With regards to the indications, treatment of active disease and prevention of relapse…"* Unchanged. The most relevant treatment goal is induction of remission.
Section 3.3.2, second paragraph, line 3	See above	Replace "It is recommended to study induction of remission and prevention of relapse in separate trials." By *"It is recommended to study treatment of active UC and prevention of relapse in separate trials."* Unchanged. The most relevant treatment goal is induction of remission.
Section 3.3.2, second paragraph, lines 7-9	It is stated: *"If only remitters to the trial drug are allowed to enter and/or are evaluated for maintenance of remission (enrichment design), the labelling will reflect this".*	Unchanged. This is outside the scope of the Guideline.

	It should be clarified as to how the label will reflect the fact that only trial drug remitters enter the maintenance of remission trials.	
Section 3.3.2, third paragraph	The impact of studying more than one sub-group (with a separate estimation of size effect for each group) on the labelling should be addressed here.	Unchanged. This is outside the scope of the Guideline.
Section 3.3.2., third paragraph, line 1	See above	Replace "Apart from the aim of either induction of remission or prevention of relapse…" by "*Apart from the aim of either treatment of active disease or prevention of relapse…"* Unchanged. The most relevant treatment goal is induction of remission.
Section 3.3.2, third paragraph, lines 2-3	Should clarify again that extent of disease can also be established based on historic patient data.	*…i.e. the anatomic extent based on medical history or endoscopy and the clinical severity of the disease.* Unchanged. The extent of disease is one of the major determinants of management and response to treatment and therefore has to be documented at entry except for studies focusing on distal disease only.
Section 3.3.2, third paragraph, lines 5-6	*'Patients with proctitis/proctosigmoiditis will usually be studied separately as local treatment forms the mainstay of treatment for these patients'.* Is this sentence meant to limit or prohibit the study of systemic therapy in patients with treatment-resistant proctosigmoiditis?	Endorsed and clarified
Section 3.3.2, third paragraph lines 6-9	It is stated: "*Disease severity can be classified into 3 main categories, mild, moderate and severe UC (see 3.1.1). Inclusion of patients into Phase III trials should preferably be limited to only one of these categories. Alternatively 2 categories may be included (e.g. moderate to severe) but in that case the study should allow for separate estimation of effect size in both groups"*. Individual Phase III trials according to severity of disease are not justified and it should be clarified what is meant by the fact that "*study should allow for separate estimation of effect size*" if mild to moderate ulcerative colitis patients are included.	Endorsed and clarified
Section 3.3.2.1, first paragraph, line 2	As mentioned above, while induction of remission certainly is one important indication, treatment of acute exacerbations (i.e. improvement of symptoms) is also a valid indication.	Replace "…and the aim of the trial, induction of remission versus prevention of relapse, …" by *"…and the aim of the trial, treatment of active UC versus prevention of relapse,*

		…" Unchanged. The most relevant treatment goal is induction of remission.
Section 3.3.2.1, second paragraph	Placebo control: It should be acknowledged that placebo control in the UC setting does not mean that the patients are on no medication (they will continue to use background medication as appropriate). Hence placebo control may be appropriate even in a study in first line use.	Unchanged. Placebo control is accepted in the add-on setting
Section 3.3.2.1, second paragraph, lines 1-2	Placebo controlled studies should also be acceptable in moderate disease given the significant placebo response rate in UC (for example see Su et al, Gastroenterology Feb 2007, Vol 132:516-26 according to which the average placebo response rate is ca. 20 % in moderate disease)	Replace with: '*For a first line indication, placebo controlled studies are not acceptable in severe active disease or for the prevention of relapse and should be justified in mild or moderate active disease'.* Unchanged
Section 3.3.2.1, third paragraph lines 5-7	It is stated: "*The option of a 3-arm trial with placebo and an active comparator, where the latter would serve as an internal reference may be acceptable in certain circumstances, e.g. when the size of a non–inferiority trial is a problem*". As the term "problem" can be open to interpretation it would be more appropriate to use the term "impractical" in this section..	Amend to: "*The option of a 3-arm trial with placebo and an active comparator, where the latter would serve as an internal reference may be acceptable in certain circumstances, e.g. when the size of a non–inferiority trial is impractical*". Endorsed and amended
Section 3.3.2.1, third paragraph, bullet point "Induction of remission", lines 1 and 2	As mentioned above, while induction of remission certainly is one important indication, treatment of acute exacerbations (i.e. improvement of symptoms) is also a valid indication.	Line 1: Replace "*Induction of remission*" by "*Treatment of active UC"* Line 2: Replace "For induction of remission in severe UC systemic corticosteroids should be used." by "*For treatment of active disease in severe UC systemic corticosteroids should be used".* Unchanged. The relevant treatment goal is induction of remission.
Section 3.3.2.2, first paragraph	The inclusion of detailed information on the primary efficacy endpoint seems misplaced in the duration of studies section and should instead be moved (with greater clarification on the endpoint) to section 3.2.2.	Delete: Once obtained remission should be maintained throughout the duration of the induction study. Earlier observations can be made for response e.g. after 2-4 weeks. Endorsed and amended

Section 3.3.2.2., first paragraph	Studies in active UC of 6 weeks durations have proven to show significant treatment benefits over active comparator or placebo; therefore and particularly in a placebo controlled setting, shorter study durations of 6 weeks should be allowed. Secondly, as mentioned earlier, induction may not be the only goal of treatment	Replace section title "Studies for induction of remission" by *"Studies for treatment of active UC".* Unchanged. The relevant treatment goal is induction of remission. And replace following sentence "Duration of induction studies should be 8 to 12 weeks." by *"Duration of studies treating active UC should be 6 to 12 weeks."* Partly endorsed and clarified
Section 3.3.2.2. , second paragraph"	Maintenance of remission studies of 6 months durations have proven to show significant differences vs. active comparator or placebo; therefore shorter study durations of 6 months should be allowed.	Replace "The duration of maintenance studies should be at least 1 year." by "*The duration of maintenance studies should be at least 6 months."* Unchanged. A minimum of 12 months duration is required for Phase III Unchanged. A minimum of 12 months duration is required for Phase III trial in maintenance of remission both for efficacy and safety.
Section 3.3.2.2, second paragraph'	*A minimum of 12-week follow-up off treatment is recommended or alternatively a randomised withdrawal phase may be added.* Rather than mandating the length of follow-up, the period should ideally be determined by the pharmacokinetics/pharmacodynamics of the drug and as such, is better measured during a randomised withdrawal phase.	Endorsed and amended
Section 3.3.2.3, third paragraph, lines 3-4	The requirement for corticosteroid use at baseline in moderate and severe disease (second line therapy) should be removed or it should be further clarified what is meant by this requirement.	Delete*:* For a second line indication in moderate and severe disease, corticosteroid use baseline is a requirement. Partly endorsed and clarified
Section 3.3.2.3, third paragraph, lines 4-6	The sentence on the widespread previous use of corticosteroids and 5-ASA adds little to the understanding and therefore should be removed.	Delete: Such previous use should not be confounded with refractoriness. Unchanged. This is an important clarification.
Section 3.3.2.3, third paragraph	Advice on how to deal with concomitant treatment in the statistical analysis would be helpful in this section.	This is too specific for a guideline. Unchanged.

Section 3.3.2.3	Intolerance to AZA/6-MP is not mentioned. It may explain why patients are not receiving these concomitant medications. This should be addressed in the guidance.	Endorsed and amended
Section 3.3.2.3. fifth paragraph, line 3	Methotrexate treatment should be added.	Replace "If bridging to AZA/6-MP is the purpose of the trial,…" by "*If bridging to AZA/6-MP or Methotrexate is the purpose of the trial,…"* Unchanged. MTX data insufficient.
Section 3.3.2.3., sixth paragraph, line 4	Selective NSAIDs or a cardiac NSAID dose should be allowed as there is no evidence that those impact the severity of the disease	Replace "…NSAID and opioid drugs should not be allowed" by *""… non-selective NSAID and/or NSAIDs used beyond the cardiac dose as well as opioid drugs should not be allowed"* Unchanged. Acetylsalicylic acid is not NSAID. No change necessary.
3.3.2.1	Choice of Comparator…Active Control…Maintenance of remission:	There is an inconsistency between these two paragraphs. In the Active control paragraph EMEA states that an active control should reflect standard practice and approved indication, and in the Maintenance of remission paragraph AZA/6-MP is recommended despite not being approved for this indication. Unchanged. Standard treatment is not dependent on approval
3.3.2	Apart from the aim of either induction of remission or prevention of relapse, there are in clinical practice two major factors that decide the therapeutic approach, i.e. the anatomic extent and the clinical severity of the disease.	Sub-population analyses based on disease extent seems to be a costly approach, and moreover disease extent is partly a function of time. Unchanged, please see above
Section 3.3.2 Paragraph 1	The sentence "In general, 2 well-conducted Phase III trials will be needed for approval." allows for different interpretations since there is no further guidance given as to how this rule should be specifically applied in relation to different development program designs . For instance, if an applicant studies both induction as well as maintenance, or different routes of administration etc.	Unchanged. This is a requirement for all new indications.
Section 3.3.2	Main therapeutic studies	We recommend that this statement should be removed from

	The Guideline states, *"Disease severity can be classified into 3 main categories, mild, moderate and severe UC. Inclusion of patients into Phase III trials should preferably be limited to only one of these categories. Alternatively 2 categories may be included (e.g., moderate to severe) but in that case the study should allow for separate estimation of the effect size in both groups."* On the basis of our experience, we believe that the inclusion of patients at single levels of disease severity into separate trials is not a generally practical approach. While it is reasonable and expected to stratify patients by disease severity *post hoc* (during data analysis), it will be extremely difficult to recruit sufficient numbers of patients at each level of disease severity in order to show a significant difference between the groups within a reasonable length of time. Moreover, this approach has not been used in the development of any drug licensed for the treatment of UC in the EU	the Guideline, and reliance placed on stratification of drug responses by disease severity. Partly endorsed and clarified
Section 3.3.2.1	<u>Choice of comparator – Active control – Induction of remission</u> The Guideline states, *"For induction of remission in severe UC systemic corticosteroids should be used."* We consider that systemic corticosteroids are not an appropriate active comparator for most biological therapies if they are tested in a conventional, parallel-group study design. Corticosteroids will generally have superior efficacy in the short term but their side effects are very undesirable. Therefore, the sponsor must either accept the study drug appearing to be less effective than the comparator or continue the study, and the side effects of corticosteroid treatment, until sufficient time has elapsed for the efficacy of the biological treatment to become apparent. However, corticosteroids could be an appropriate control, even for a biological therapy, in an "add-on" trial design. We would recommend that the Guideline be amended to state that corticosteroids should only be used as a comparator for biological treatments in an "add-on" study design. This design should be preferred for the induction of remission in severe UC.	Partly endorsed and clarified
3.3.1	For proof of concept studies, endoscopy should be included in the prima outcome measures	Unchanged. Already explained
3.3.2 Main therapeutic studies	Correct the terms for disease distribution (as per 3.1.1, above)	Endorsed and amended

P3 L5		
P3 L8	Suggest that the example in brackets is 'mild to moderate', not moderate severe, since severe colitis is usually treated in hospital, as indicated paragraph The separation of proctosigmoiditis from more extensive forms of dise **should not** be mandatory. Some patients with proctosigmoiditis may ne systemic therapy as well as is the case for AZA. Non-response to therapy as an indication for refractory disease should not limited to steroids, what about AZA? Infliximab?	2 first points endorsed and amended. Third point partly endorsed, however infliximab is a third line treatment
3.3.2.1 Choice of compara P1 L4	Correct term 'proctitis/prctosigmoiditis to 'distal' to be consistent with 3.1.1	Endorsed and amended
3.3.2.1 Induction of remission	Correct terminology to conform with 3.1.1 Placebo acceptable only for add on trials since in second line treatment the patient population would have a more active disease despite a previous treatment failure. For induction of remission of severe disease infliximab or cyclosporine can also be used for comparison	Endorsed and amended Unchanged. There is no widely accepted second line treatment Unchanged. The guideline does not prevent the suggested comparison. However it is not considered appropriate to replace placebo comparison.
3.3.2.2 Duration of studies	*…remission* Change to 'Duration of studies should be 4-12 weeks. T primary efficacy endpoint, the rate of steroid-free remission, should evaluated at 4-8 weeks…. (This is still consistent with the need to ta steroids in a standardised manner, para 3.3.2.3)	Partly endorsed and clarified. Study duration should normally be 8-12 weeks, but dependent on the PD properties of the study drug, could be shorter.
	3.3.2.3 Previous and concomitant treatment P3 L3: add 'at' before 'baseline' P3 L6: Change 'confounded' to 'confused' P4 L2: Use a decimal point, not a comma (2.5 to 5mg/week..) P5 L2: '…allow this kind of treatment if the prime purpose is to evaluate effect of oral or systemic therapy.' State that Prednisolone is equivalent for steroid use	Partly endorsed and amended

3.4 STUDIES IN SPECIAL POPULATIONS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
3.4.3, second paragraph	The inclusion of pouchitis as a sub-group of UC is questioned, since this is normally treated with antibiotics. Hence products being developed for UC are unlikely to have an effect.	Unchanged. Pouchitis is an important complication of UC
3.4.2 Studies in children… P2 L1	Add 'with UC' after 'patients'	Endorsed and amended
3.4.3 Studies in other subgroups	Subheading '*Fulminant'*: Change to 'Acute severe colitis' (see above)	Endorsed and amended
P1 L1	Insert after first sentence 'The definition of acute severe colitis m commonly used is that of Truelove & Witts'. This remains the simplest, b validated and most widely used index for identifying severe ulcerative coli any patient who has a bloody stool frequency ≥6/day and a tachycar (>90bpm), *or* temperature >37.8°C, *or* anaemia (haemoglobin <10.5g/dL), an elevated ESR (>30mm/hr) has severe ulcerative colitis. [Truelove S Witts LJ. Cortisone in ulcerative colitis: final report on a therapeutic trial. *Med J* 1955; **ii:**1041-1048.] This index has been used in 20/32 studies intensive intravenous treatment for severe ulcerative colitis [Turner D, et Response to corticosteroids in severe ulcerative colitis: a systematic review the literature and a meta-regression. *Clin Gastroenterol Hepatol* 2007**;5**:1(10].	Endorsed and amended
P1 L4	Change to 'Intravenous steroid-refractory colitis may be defined us validated indices that predict colectomy in this population, eg the Oxfo index or the Swedish fulminant colitis index…' (appropriate references Travis SPL, et al. Predicting outcome in sev ulcerative colitis. *Gut* 1996;**38:**905-910 and Lindgren SC, et al. Ea predictors of glucocorticoid treatment failure in severe and moderately sev attacks of ulcerative colitis. *Eur J Gastroenterol Hepatol* 1998; **10:**831-5].	Partly endorsed and amended
P1 end	Amend 'Avoidance of colectomy short-term ad long-term are relev primary endpoints in this population, and quality of life over an extend period is a relevant secondary endpoint.'	Endorsed and amended

Extraintestinal manifestations P1 L5	delete 'highly'	Endorsed and amended
3.5 CLINICAL SAFETY EVALUATION		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Section 3.5	Clinical safety evaluation: The safety section is very general and doesn't contain much information specific to UC. Further detail on any points of particular relevance to UC would be helpful. In addition, advice on dealing with assessing the safety profile of a product when most of the data comes from trials with active comparators and where there is a high level of background disease would be useful in this section.	Unchanged. Only issues of general relevance to the disease can be included. The most important safety aspects related to UC have already been included.
Section 3.5.1, second paragraph	The two paragraphs in this section on immunomodulatory agents should be combined into one to aid clarity and avoid repetition.	Amend to: *"For drugs with an immunomodulatory action, risk of neoplasia, infections and autoimmune disease is of particular interest. Further and full assessment of this effect could be done post marketing."* Endorsed and amended
Section 3.5.2 , first paragraph	Duration of studies: The paragraph on immunomodulators does not fit well in this section. Instead it should be combined with the second paragraph in section 3.5.1.	See above for wording recommendation for section 3.5.1 / 2nd paragraph. Endorsed and amended
3.5.2 Duration of Studies	At the time of marketing authorization, it is expected that safety data of a least 1 year are available for a meaningful number of patients	It would be helpful to get some guidance on the meaning of "a meaningful number of patients." Can a smaller number of patients with a longer period of drug exposure (over 1 year) be an acceptable alternative to a larger patient population with a shorter (at least 1 year) period of drug exposure in Phase II and /or Phase III trials. Can SAFETY data from another IBD indicated clinical trial (using the same study drug) be used to supplement the safety data being collected from the UC study, such that the additive number of patients from both studies fulfills "the meaningful number of patients"? Unchanged. The general requirements concerning size of safety database are mentioned in the ICH guideline

3.5.1 Specific adverse ever P2 L1:	Change ‘is’ to ‘are’	Endorsed and amended