EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2016
CHMP/EWP/18463/2006 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis

Draft

Draft agreed by Efficacy Working Party	04 October 2006
Adopted by CHMP for release for consultation	16 November 2006
End of consultation (deadline for comments)	31 May 2007
Agreed by Efficacy Working Party	September 2007-January 2008
Adoption by CHMP	24 January 2008
Date for coming into effect	01 August 2008
Agreed by Gastroenterology Drafting Group	March 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	1 August 2016
End of consultation (deadline for comments)	31 January 2017

This guideline replaces' guideline on the development of medicinal products for the 8 treatment of ulcerative colitis' (CHMP/EWP/18463/2006)

Comments should be provided using this template. The completed comments form should be sent to gastroenterologydg@ema.europa.eu

Keywords	***Inflammatory bowel disease, Crohn's disease, medical treatment, clinical trials, study design, study endpoints, children, adults***

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Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis

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Executive summary

This is the 1st revision of the Guideline on the development of new medicinal products for the treatment of UC.

The main aim of this 1st revision is to update the guidance on the design of studies in adult patients, especially on potential claims, primary and secondary endpoints and comparators. It is also intended to give further guidance with regards the possibility for extrapolation from adults, or the need to generate separate data in children and to give recommendations regarding the exploration of PK/PD in paediatric drug development.

1. Introduction (background)

UC is a chronic, relapsing inflammatory bowel disease affecting the colon. The prevalence is estimated to be 70-500 cases per 100.000 with peak age of onset between 15 and 25 years. In 15% of cases UC is diagnosed in childhood and may present before school age. The disease involves the rectum and may extend continuously proximally to involve part of or the entire colon. The mainstay of therapy for mild to moderate UC is 5-aminosalicylic (5-ASA) agents. These agents are effective at inducing remission in UC and in maintaining remission in UC. The majority of patients with moderate to severe active UC benefit from topical, oral or parenteral glucocorticosteroids. Remission, however, cannot be maintained with steroids. Azathioprine (AZA) or mercaptopurine (MP) has been employed as glucocorticoid-sparing agents in patients unable to be weaned from glucocorticoids. Anti-tumour necrosis factor α (TNF) agents and integrin inhibitors are indicated for the treatment of UC patients refractory to standard treatment (as previously described). Surgery with colectomy is curative but can be associated with significant morbidity and is thus reserved for acute severe (fulminant) colitis or resistant cases and in some cases as cancer prevention. Intestinal continuity can be restored by construction of an ileal pouch-anal pouch anastomosis.

Pouchitis is an inflammation of the ileal pouch, occurring in up to 20-30% of patients with an ileal pouch-anal anastomosis. The risk of colorectal cancer is increased in patients with extensive disease and surveillance is usually introduced after 8-10 years of disease duration with regular colonoscopies. Extra-intestinal manifestations of UC include primary sclerosing cholangitis, as well as eye, joint and skin manifestations.

2. Scope

Guidance is provided on the EU regulatory position on the main topics of the clinical development of new medicinal products in the treatment of patients with UC. This document is aimed to replace the 'Guideline on the development of new medicinal products for the treatment of UC' (CHMP/EWP/18463/2006).Generic drug development is not covered.

The current revision concerns a major update of the guidance document with regards to the issues mentioned in the executive summary above.

3. Legal basis and relevant guidelines

This Guideline should be read in conjunction with the introduction and general principles of Annex I to Directive 2001/83/EC, as amended, and all other relevant EU and ICH guidelines. These include, but are not limited to:

- Points to Consider on Multiplicity Issues in Clinical Trials (EMA/CPMP/EWP/908/99).

- Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99).
- Reflection Paper on the regulatory guidance for the use of Health-Related Quality of Life (HRQL) measures in the evaluation of medicinal products (CHPM/EWP/139391/04)
- Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004 Corrigendum)
- Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005).

4. Criteria and Standards for Patient selection

4.1. Definition and specification of the disease

4.1.1. Active UC

UC is a chronic, inflammatory disease of the large intestine and rectum characterised by episodes of increased stool frequency and bloody diarrhoea. Patients complain of pain (abdominal cramps), urgency and bloody diarrhoea. The diagnosis of UC should be based on patient signs and symptoms (diarrhoea and rectal discharge of blood and/or pus), endoscopic findings (continuous oedema, friability, granularity and ulcerations in colorectal mucosa), and histological findings (crypt distortion/abscess, ulceration). Infectious causes of colitis and malignancy must be ruled out. Depending on the extent of disease, patients can be classified (according to the Montreal classification) as having 1) ulcerative proctitis involving only the rectum (E1), 2) left sided UC involving the colorectum distal to the splenic flexure (E2) and 3) extensive UC (E3) involving the colon proximal to the splenic flexure (includes pancolitis). Up to 30% of patients with distal disease will experience proximal extension with time. Depending on the disease activity, patients can be classified as having mild, moderate or severe disease activity according to one or more measures of disease severity. Patients with acute severe UC not responding to steroids represent a special subgroup.

4.1.2. Steroid dependency

In line with current published European guidelines (European Crohn's and Colitis Organisation (ECCO)), patients exhibiting response to steroids who

i. are unable to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months of starting steroids, without recurrent active disease, or

ii. have a relapse within 3 months of stopping steroids

can be considered steroid dependent.

4.1.3. Refractory disease

Patients who continue to have active disease despite the use of corticosteroids in an adequate dose and for an adequate time period are defined as being steroid refractory. According to published European guidelines (ECCO), patients who have active disease despite prednisolone up to 0.75 mg/kg/day over a period of 4 weeks can be characterised as having steroid refractory disease. Patients are refractory to azathioprine/6-mercaptopurine if they continue to have active disease despite at least 3 months of treatment with a sufficient dose.

4.1.4. UC in remission

Patients with mucosal healing (MH) (for the purpose of this guideline MH is defined as absence of macroscopic signs of active inflammation as judged by endoscopy) who have no or very mild symptoms and signs are considered in remission. The precise definitions depend on the instruments used to assess mucosal inflammation and symptoms (please see below).

5. Indications/treatment goals

In order to obtain an indication for "treatment of active ulcerative colitis", efficacy in both "induction of remission" as well as "maintenance of remission" should be demonstrated

Depending on the properties of the drug (i.e. not suitable for long term treatment or not suitable for acute treatment) separate indications for "induction of remission" or "maintenance of remission" may be granted.

The treatment of active disease/induction of remission, and the treatment for maintenance of remission/prevention of relapse may be studied either in separate trials or trials that combine induction treatment with maintenance treatment. While a "treat through" design may be acceptable the design of the study will have implications for the indications that can be claimed. Only separate investigation of induction of remission and maintenance of remission would allow claims for separate indications for induction and maintenance of remission.

Other claims such as steroid sparing and improvement in quality of life should not form a part of the indication, but may be included in other relevant section(s) of the prescribing information. However, the ultimate treatment goal for all patients with UC is steroid-free clinical and endoscopic remission.

6. Assessment of efficacy

6.1. Methods to assess efficacy criteria

New drugs intended for the treatment of UC are expected to provide symptomatic relief to the patient based on a documented effect on the inflammatory process. Apart from demonstrating that the symptomatic effect is indeed related to a positive effect on the disease process the latter element is considered essential as there is evidence that lack of control of inflammation even in the presence of control of symptoms is correlated with poor long term outcome.

Symptomatic relief should be evaluated by patient related outcomes (PRO). There are a number of clinical indices, e.g. SCCAI (simple clinical colitis activity index) mainly including patient reported symptoms. Whereas these may be used provided that they are adequately validated, this guideline recommends the further development and validation of PRO instruments for the use as primary outcome parameter in clinical trials in UC. Such an instrument should include clinically important signs and symptoms of UC, e.g. increased stool frequency and rectal discharge of blood. An instrument to be used as primary outcome measure in pivotal clinical trials in UC should be completely and rigorously validated.

Whereas symptomatic relief is best evaluated by patient reported outcomes, the effect on the inflammatory process as such should be evaluated directly by endoscopy. A number of different indices have been used for grading endoscopic disease activity. UCEIS (UC endoscopic index of severity) and the endoscopic part of the Mayo score appear to be the best, albeit not fully, validated scores.

A significant effect on both aspects of the disease is required (co-primary endpoints). Composite indices including both symptoms and MH, such as the Mayo Clinic index have been used in several clinical trials. The use of this index may be justified, however, as previously mentioned, an effect on both the patient related sub-score and the endoscopic score is expected. It has to be stressed that the total Mayo score including physician's global assessment is not of primary interest.

Surrogate markers of inflammation, such as CRP and faecal calprotectin are considered supportive but cannot replace direct endoscopic evaluation of inflammation.

6.1.1. General Aspects

6.1.1.1. Primary endpoint

Achieving/maintaining remission free of steroids is an appropriate primary end-point. In patients receiving systemic steroids these should be tapered according to predefined schedules. For induction studies of short duration requiring early evaluation of efficacy a low dose of steroids may be acceptable provided that the dose is clearly justified and pre-specified.

Remission should be defined and justified according to the instruments used for evaluating signs and symptoms and inflammation, respectively. E.g. when mucosal inflammation is evaluated by the Mayo sub score, a score of 0 or 1 may be used for defining endoscopic healing. Whereas the more stringent definition is preferred, the less stringent definition could be acceptable, based on the pharmacodynamic (PD)-properties of the investigational compound and/or the patient characteristics (e.g. severity).Adjudication of endoscopic evidence of activity should be performed, preferably by central reading of the examinations. If decentralised reading of examination is performed, standardization of reading should be convincingly demonstrated. Correspondingly, when clinical symptoms are evaluated using the clinical part of the Mayo score, a score of 0 or 1 may be used to define symptomatic remission.

Irrespective of scale used, the definition of remission should encompass cessation of rectal bleeding.

As outlined above, symptomatic remission and MH should be considered co-primary endpoints. However, as listed below, achieving both symptomatic remission and MH (for the individual patient) is considered an important secondary endpoint. The timing of measuring the primary endpoint depends on the aim of the treatment (please see below) as well as the pharmacodynamic properties of the test drug.

6.1.1.2. Secondary endpoints

- Patients achieving both MH and symptomatic remission
- Patients achieving response. Response should be defined according to the instruments used for evaluating symptoms and inflammation, respectively.
- Patients achieving remission defined differently from the primary evaluation (if the less stringent evaluation regarding MH is chosen, the more stringent should be used in the secondary evaluation, and vice-versa)
- Numerical evaluations of the symptom score, and of MH
- Histological evaluation of mucosal inflammation, including number of patients achieving histological normalisation
- Patients achieving MH, judged endoscopically, as well as combined clinical, serological (=normalisation of CRP and/or calprotectin) and histological remission

- Time to remission;
- Time to response;
- Laboratory measures of inflammation (e.g. CRP, faecal calprotectin);
- Validated QoL measurement (please see EMA Reflection Paper on the regulatory guidance for the use of Health-Related Quality of Life (HRQL) measures in the evaluation of medicinal products), e.g., inflammatory bowel disease questionnaire (IBDQ);
- Steroid sparing effect such as: Proportion in steroid-free remission;
- Reduction in number of colectomies.

In patients who are steroid dependent, withdrawal of the steroids may be the objective. The primary endpoint should be the number of patients in clinical and endoscopic remission in whom steroids could be withdrawn. Procedures for withdrawal (e.g., tapering schedules) should be predefined.

Even though separate trials in mild to moderate and moderate to severe are recommended (due to differences in comparators), it is recommended to use a stratified randomisation according to disease activity as judged by mucosal inflammation, e.g. mild, moderate and severe. The response with regard to intestinal and extra intestinal symptoms and findings should be measured individually in all patients to determine possible predictors to response and failure. Efficacy should be analysed according to prospectively defined disease and patient characteristics. Mode of delivery into the intestines for locally acting drugs should be taken into account.

7. Study design

7.1. Pharmacology studies

7.1.1. Pharmacokinetics

The pharmacokinetic properties of the medicinal product should be thoroughly investigated in accordance with relevant guidelines regarding interactions, special populations (elderly and paediatric, renal and hepatic patients), and specific quality aspects (locally applied drugs, proteins and monoclonal antibodies).

7.1.2. Interactions

Interaction studies should be performed in accordance with the relevant guidelines. Efficacy and safety implications of concomitant drugs likely to be co-administered in clinical practice (e.g. glucocorticoids, immunosuppressants) should be evaluated.

7.2. Therapeutic studies

7.2.1. Dose finding studies

For the dose response ICH E4 guidance Dose-Response Information to Support Drug Registration should be considered. Evaluation of multiple doses is recommended. Placebo controlled, randomized, double blind and parallel group design is recommended. Duration of the phase II dose finding study depends on the indication sought (induction of remission and/or maintenance of remission) as well as pharmacodynamic properties/safety profile/mode of action of the drug and the chosen endpoints but should generally not be shorter than 6-8 weeks.

7.2.2. Confirmatory studies

7.2.2.1. Treatment of active disease / Induction of remission

7.2.2.1.1. Design elements

In active UC, the design should be a randomised double blind parallel group comparison. In the absence of withdrawal of consent, clinical deterioration or failure to improve (according to pre-defined definitions for treatment failures), treatment under double-blind conditions should continue until the completion of the active treatment period. In the absence of withdrawal of consent, all patients should complete the pre-specified follow-up period for the study. Escape procedures for non-responders should be included in the protocol (especially when a placebo-control is included in the trial), which should secure a meaningful comparison of the treatments. Whereas unavoidable from a ethical point of view, a high number of patients receiving rescue medication may be undesirable from a methodological point of view and may be particular problematic in non-inferiority studies where assay sensitivity may be lost.

In general, in order to demonstrate durability of response, active treatment should continue for 8 weeks. However, based on the pharmacokinetic and pharmacodynamic properties (including mode and speed of onset of action) of the new compound, a shorter/longer duration may be justified. Longer study duration may be justified depending on the onset of action of the drug. However in order to provide a useful intervention for acute active disease, symptom control is expected within 4 weeks. An appropriate follow-up period off therapy is recommended to see if patients who are in remission at the end of treatment remain in remission at the end of follow-up, unless the patients are continuing the treatment in a re-randomised or continued maintenance study. Patients on steroids at entry should have their dose tapered according to predefined tapering schedules. Obtaining steroid-free remission should be the goal of therapy. .As previously stated, if efficacy is evaluated at an early time point, a low dose of steroids in remitters may be acceptable provided that this is adequately justified and pre-specified. In case efficacy is evaluated at multiple time points, the primary time point for analysis should be pre-specified and justified (please refer to Points to Consider on Multiplicity Issues in Clinical Trials). Evaluation of rebound after tapering of steroids should be evaluated.

7.2.2.1.2. Patient selection / target population

Failed prior therapies and on-going treatment should also be taken into account.

Patients included should have evidence of active disease as outlined in section 4. Minimal levels of symptoms and mucosal inflammation needed for inclusion should be defined. Degree and extent of mucosal inflammation should be documented by recent visualisation of the gastrointestinal tract, by endoscopic examination.

As there are currently no fully validated PROs, a score of 6-12 in the clinical part of the Mayo score may be used as an inclusion criterion but patients included must also have a certain minimal level of mucosal inflammation (e.g. a score ≥ 2 when using the endoscopic part of the Mayo score).

The choice of study population should reflect the proposed indication. Patients included should be well characterised especially as regards disease extent (proctitis, left-sided or extensive), duration, disease activity, prior treatment and smoking status. The minimum time from diagnosis should be at least 3 months at inclusion. Shorter duration of disease has to be justified and care must be taken to avoid inclusion of patients with diarrhoea due to other causes e.g. infections and Crohn's disease.

7.2.2.1.3. Choice of endpoints

Please refer to “General Aspects” above. The primary endpoint should be steroid free remission.

7.2.2.1.4. Choice of comparator

The choice of comparator will depend on the indication for which the drug is being developed. In order to support a first line indication in the treatment of active UC, it is necessary to demonstrate that the drug has either the same or an improved risk/benefit profile as the standard of care. Therefore, clinical trials aiming at supporting a first line indication should always include comparison with the accepted first line treatment. Unless the study is aiming at demonstrating superiority against an existing treatment, it is critical that assay sensitivity can be demonstrated, ideally by adding a placebo arm (ref. ICH E10).

In order to support an indication for add-on to established therapy, the drug should be compared with add-on placebo. For a second-line indication in patients with insufficient response to established therapy, it is advised that the established therapy is continued and placebo or experimental therapy is added on. Failure of the background treatment should be clearly defined. In this respect, merely having previously been exposed (without documentation of insufficient response) to one or more first line drug is not considered sufficient.

<u>First line treatment (treatment naïve patients):</u>

<u>Mild to moderate disease</u>

For mild to moderate active UC, oral and/or topical 5-ASA (depending on the extent of the disease) is a well-established safe and efficacious treatment for both induction and maintenance of remission.. Superiority against the comparator is the ideal requirement. Non-inferiority against 5-ASA is also acceptable. However, the option of a 3-arm trial with placebo and an active comparator, where the latter would serve as an internal reference (not requiring formal non-inferiority) may be acceptable in certain circumstances, e.g. when the size of a non–inferiority trial is impractical.

<u>Moderate to severe disease</u>

Systemic corticosteroids are considered a well-established safe and efficacious treatment in this setting. Consequently, for a first line indication for induction of remission in moderate to severe UC, any new treatment should demonstrate non-inferiority (or superiority) against systemic corticosteroids. Patients included in a study of this kind cannot be on steroids at entry.

<u>Second line treatment (treatment experienced patients)</u>

In patients who have symptomatic as well as objective active disease despite standard treatment such as 5-ASA, thiopurines and/or corticosteroids, it is clinical practice to continue standard treatment (except for corticosteroids, which generally should be discontinued at the earliest time point possible, depending on the obvious side effects already present, and the duration of the pre-treatment) and to add additional treatments. Consequently, placebo controlled add-on studies is an acceptable option in this setting. While formal (non-inferiority/superiority) comparison with TNF-inhibitors is not considered mandatory, it is encouraged. In case of targeting TNF-experienced patients, add-on, placebo-controlled studies are considered acceptable.

7.2.2.2. Maintenance of remission / Prevention of relapse

7.2.2.2.1. Design elements

The efficacy of maintenance treatment should be established by means of placebo-controlled trials. Patients in remission without any treatment should be treated with placebo or test drug. Patients who are presently on the test drug should be randomised to continuing the test drug or switching to placebo. Patients in remission while on maintenance therapy may receive placebo or test drug as add on therapy or may be randomised between continued maintenance therapy (or placebo) and the experimental compound only.

In the absence of clinical deterioration (according to pre-defined definitions for treatment failures) and withdrawal of consent, treatment under double-blind conditions should continue until the completion of the study period. For handling of missing data please refer to Guideline on Missing Data in Confirmatory Clinical Trials.

The treatment period should be aimed at a minimum of 12 months.

7.2.2.2.2. Patient selection / target population

Patients who are in steroid free remission (as defined above) are eligible for inclusion into the trials. In lack of properly validated PROs a score of 0-1 in the clinical part of the Mayo score may be used as an inclusion criterion but patients included must also have an evidence of MH (e.g. a score <2 or 0 when using the endoscopic part of the Mayo score). This should be documented by visualisation of the gastrointestinal (GI) tract by endoscopic examination.

Trials combining induction treatment and maintenance treatment should preferably only enter patients that have achieved remission (in either the trial drug or comparator group), into the maintenance phase. Responders may be included in the maintenance phase as it is considered relevant to study if continued treatment in responders may eventually lead to remission. However, if the intended claim is “maintenance of remission”, the primary analysis should be based on the remitters only. Furthermore, in order to claim maintenance of remission, a re-randomisation between phases is considered necessary. As mentioned in section 5, a treat-through design (without re-randomisation) may be acceptable and will provide evidence of the effect of long-term treatment. However, true maintenance of efficacy cannot be supported by such a trial and consequently such a trial cannot support a claim for “maintenance of efficacy”.

For combined studies aiming at supporting general treatment indication, it is required that statistically and clinically significant results are obtained for both phases of the trial.

Choice of design may be influenced by differences in dosage for induction and maintenance, respectively.

7.2.2.2.3. Choice of endpoints

It is recommended that the primary end-point should be steroid free remission maintained without surgery throughout at least 12 months. Time to event analysis is only consideres supportive as just pronlonging time to relapse without decreasing the end of study risk is not considered a relevant benefit. As secondary endpoints, reduction in surgery, quality of life (as measured by validated indices such as IBDQ, EuroQol-5D, SF36) and time to relapse could be considered. Severity of relapse should also be considered.

Relapse should be defined a priori, including the need for deterioration of a certain degree of symptoms and/or inflammatory markers, and final confirmation with endoscopy (on demand). Patients

with relapse undergoing re-treatment, or leaving the study with treatment outside the protocol should nevertheless undergo the full period of planned follow-up. Efforts should be made to obtain all relevant endpoints in all patients irrespective of treatment adherence.

Please also refer to “General Aspects” above.

7.2.2.2.4. Choice of comparator

The choice of comparator depends on the indication for which approval is being sought. For a first line indication of maintenance of remission, the efficacy of maintenance therapy in this patient population should be determined by placebo-controlled trials if ethically justifiable. In addition, for the refractory population, comparative studies using immunosuppressive therapies such as azathioprine and mercaptopurine (MP) or TNF-inhibitors as comparators are recommended.

7.2.2.3. Previous and concomitant treatment

Patients with UC usually receive maintenance treatment and should in general be allowed to continue with these during a trial in active disease as background therapy. The duration and dose of concomitant treatment prior to inclusion should be defined. For 5-ASA, a stable dose for > 2 weeks is appropriate for induction studies and > 4-6 weeks for maintenance studies. Treatment with AZA/MP requires stable doses for at least 3 months.

When concomitant treatment is not to be allowed, adequate washout period should be defined. For newer immunomodulating agents, that may have prolonged action, adequate washout period based on the pharmacodynamic effect of these agents should be ensured.

For a refractory population, it should be ensured that patients have received optimal treatment before randomisation. A minimum duration and dose of previous (baseline) medication should be defined. For a second line indication in moderate and severe disease, this would usually imply corticosteroid use at baseline. History of previous use of corticosteroids and 5-ASA is of little relevance, as most patients diagnosed with UC will have used these medications at some time during the course of their disease. Such previous use should not be confused with refractoriness. Corticosteroid dependency should be defined as previously specified. Intolerance should also be defined by minimum criteria of severity, e.g. previous mild and resolved side effects to corticosteroids that did not lead to discontinuation of the treatment would not classify as patient being intolerant to corticosteroids. Refractoriness to AZA/MP requires at least 3-6 months of treatment without improvement. Intolerance to AZA/MP should be clearly defined and documented.

Tapering schedules for glucocorticoids during trials should be standardised. Usually tapering can be done with 2.5 to 5 mg/week in induction studies. Too rapid tapering is to be avoided. As noted above, patients who have not been tapered before or within the induction phase should have their steroids tapered within 12 weeks after entering the maintenance phase. If bridging to AZA/MP is the purpose of the trial, the tapering of the investigational drug should be over 3 months at least.

Concomitant treatment with topical treatment in extensive disease may influence the endoscopic findings with sigmoidoscopy and thus it would be acceptable not to allow this kind of treatment if the prime purpose is to evaluate the effect of oral or systemic therapy. However, in order to reflect the real life use of compounds, ideally, both treatment modalities (cessation and continuation of local treatment) should be investigated. Antibiotics should normally be excluded and in severe disease, anti-cholinergic, anti-diarrhoeal, NSAID and opioid drugs should not be allowed as they may contribute to worsening of the relapse.

8. Safety aspects

8.1. Specific effects

Identified adverse events should be characterised in relation to the duration of treatment, the dosage, the recovery time, age and other relevant variables. A major category of products used in the treatment of UC acts as immunomodulators. Therefore special attention should be given to the possibility of occurrence of serious infections, autoimmune diseases and the tumour facilitating/inducing potential of these products. As UC affects young women of childbearing potential, special attention is warranted in this population.

8.2. Long-term effects

Given the potentially long-term use of drug therapy in UC, data on a large and representative group of patients for a sufficient period of time should be provided. The administration of new biologicals (e.g., cytokines, anti-cytokines, monoclonal antibodies) may trigger the development of antibodies. Therefore, whether binding-antibodies and/or neutralising antibodies against these products are developed and the impact of this on the long-term efficacy and safety of the product should be investigated.

Concomitant use of immunosuppressants in add-on studies may increase the risk for serious adverse events. It is important to register all use of these agents in trials with new immunological treatments. Furthermore, it is important to get information on re-treatment outcomes even after a longer time interval without treatment with a specific drug.

8.3. Studies in special populations

8.3.1. Studies in paediatric patients

Ulcerative colitis is similar in adult and paediatric patients in terms of overall disease pathology and progression and possible treatment targets. However, paediatric forms of IBD are characterised by a more complicated disease course with higher inflammatory activity and higher need for corticosteroids and immunosuppressive therapy. Subsequently children have a higher cancer risk, longer duration of disease, severity or extension of disease compared with adult-onset UC.

UC is rare in children below 10 years of age and younger children may develop a different disease phenotype compared with adolescents or adults. The clinical development program should include children from 2 years of age and older unless there are significant safety concerns or signals (occurrence of significant adverse events in juvenile animals or adults or additional immune deficiency) that preclude the inclusion of certain age groups, or unless there is evidence that the product is not likely to be effective or beneficial in certain age groups. Younger children should be genetically tested for known immunological defects and in- or excluded depending on the defect.

Due to marginal differences to adult disease inclusion of adolescents with UC into trials with adults can be considered.

In general patients with moderate to severe disease activity should be included to enable demonstration of sufficient treatment response.

8.3.1.1. Extrapolation of data

Based on similarity of the disease in adults and in children, extrapolation of efficacy or safety should be considered in order to spare children from unnecessary trials. Application of extrapolation approach may result in a reduction in the amount of data required and/or obviate the need for a formal efficacy trial. An extrapolation plan for paediatric development should be constructed where relevant, addressing the identified knowledge gaps and defining the amount of new data needed (modelling and simulation, size of trial population, focus on subpopulations or certain age groups only, exploratory/confirmatory design of the study, randomised withdrawal, single-arm or uncontrolled trial…). Usually, extrapolation has to be based at least on efficacy and safety established in adults and paediatric pharmacokinetic and pharmacodynamic data (including the PK-PD and exposure-response relationship).

To justify and develop the extrapolation plan, the following factors will need to be considered carefully on a case by case basis:

- Whether the substance belongs to a well-studied pharmacological class for which several substances have already been granted a paediatric indication
- Whether a comprehensive amount of data has already been collected in adults with UC
- Whether a safe dose in children has been identified for the same medicinal product for other diseases.

Age, body weight, growth and sexual maturation should be taken into account for specification of the extrapolation plan.

Extrapolation assumptions should be confirmed by re-evaluation of the extrapolation concept during development and by post-authorisation collection of real world safety and effectiveness data.

8.3.1.2. Pharmacokinetic and dose finding studies in paediatric patients

It is well known that age-related differences in PK may be very large and non-linear, especially when inclusion of the youngest age groups is considered. As explained in more detail in the Guideline on the role of the pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004 Corrigendum) in the paediatric studies the starting dose per age or weight group and final dose should be selected taking into account all available PK, PD or other (preliminary) data from adults and/or children. In contrast to the PK Guideline it is preferred to apply population PK modelling on the basis of all available data, because this approach allows for an extensive covariate analysis in which the influence of weight, age and other covariates is quantified. The results of this covariate analysis can be used in case a certain exposure (AUC or Ctrough) for instance from adults is aimed for, to identify whether different mg/kg doses per age group may be needed to define to reach the same exposure across the entire paediatric age range, given the fact that the PK may change in a non-linear manner with weight.

In addition to the optimisation of posology for subgroups in which the exposure differs from the overall study population and/or is more difficult to predict (i.e. the lower part of an age range), it is emphasized here that particular attention should be paid to the entire age range including the extremes of age receiving the specific product. In addition to the PK Guideline dose adjustments should be allowed in case of sub-target trough or AUC levels to adjust for remaining (inter individual) variability, as there is increasing evidence in adults that precision based dosing may increase efficacy of treatment. Also recommendation on the need for individual dosing and dose adjustment in case of

sub-target trough or AUC levels in non-responders should be made based on the results obtained during studies.

8.3.1.3. Efficacy in paediatric patients

Studies in children should aim for achieving remission without side effects on growth and maturation. Remission should be defined as clinical remission accompanied by endoscopic MH. Clinical remission and endoscopic MH should be used as co-primary endpoints.

Clinical response alone in children is not considered acceptable as primary endpoint in respect of the longevity of the disease in this age group and colectomy with an ileo-anal pouch as alternative.

For induction/ maintenance trials representative changes in mucosal appearance are expected to be evaluated, therefore endoscopy is required.

Endoscopic MH should be assessed by the Mayo score (score of 0, or ≤1). Because a validated paediatric PRO (pPRO) for the evaluation of symptoms is not currently available, for the time being, the use of the PUCAI as a surrogate for symptomatic remission is considered acceptable. Clinical remission can therefore be defined as PUCAI<10 points.

The primary endpoint of maintenance trials should be sustained relapse-free corticosteroid-free remission (defined as maintaining both, symptomatic clinical remission, and endoscopic MH).

In trials when endoscopy is waived, the primary outcome measures should reflect the percentage of patients achieving or maintaining corticosteroid-free remission. Due to the sufficient amount of validation data available with good results, the PUCAI score can be used in such a situation, with remission defined as a PUCAI score of <10 points.

8.3.1.4. Strategy and design

As stated previously extrapolation can facilitate paediatric development and may result in a reduction in the amount of data and/or change in study design required in certain age groups (see 8.3.1.1.). In situations where extrapolation of efficacy is not possible, the parallel group design provides the most robust evidence for efficacy and safety and is the preferred design. Ideally, randomised placebo or active comparator controlled trials (RCT) should be conducted for efficacy evaluation.

There are ethical concerns about the use of placebo when safe and effective alternative treatment is available. Two-arm non-inferiority studies without a placebo-arm could be acceptable provided that the selected comparator can be justified on the basis of a well-established efficacy, and an appropriately justified non-inferiority margin can be predefined. Such comparative studies must have assay sensitivity (see Guideline on the choice of the non-inferiority margin, EMEA/CPMP/EWP/2158/99).

In case the use of a placebo control group is considered necessary all efforts need to be made to assure that the patient is not exposed to more than minimal risk. For example, randomisation can be set with unequal allocation with fewer patients in the placebo arm, especially in case where there is a control active treatment arm in the trial. Patients in the placebo arm are not left untreated, as standard of care medication will be available to all patients recruited in the trial.

It is acknowledged that there is a limited pool of patients available for clinical trials in UC and combined trial designs for induction and maintenance of remission can be accepted. Nevertheless the design has to be adapted to allow interpretation of results in both phases and an element of dose-comparison may be built into a maintenance phase considering that the dose may not be the same for achieving as for maintaining remission.

8.3.1.5. Safety in paediatric patients

Collection of safety data will always be required to identify any unexpected age-specific safety events. For the confirmation of efficacy and to evaluate safety in larger populations long-term post-marketing observational studies (i.e. registries) may be used.

Special attention should be paid to the fact that the spectrum of adverse reactions might differ in children in comparison to adults. Therefore drug levels should be taken into account. Post-study/post-authorisation long-term data, either while patients are on chronic therapy or during the post-therapy period, are necessary to determine possible effects on maturation and development.

If there are concerns on the medicine's impact on the immune system that cannot be addressed in the pre-clinical development or by studies in adults but can be answered by clinical studies in children (development of immune system, response to vaccination, etc.), appropriate studies or sub-studies should be conducted. This is particularly true for a drug with new mechanism of action to be tested in younger children (e.g. less than 6 years old) where adequate measures to evaluate the potential impact of the experimental therapy on vaccination should be implemented.

The long-term evaluation of safety requires collection of data from larger number of patients for a longer period of time, potentially into adulthood. Long-term safety could be studied in open label extension studies and in post-marketing observational registry-type studies. The protocols for such studies should define and record the risks of the medicinal product. The registry should preferably be an established disease-based (rather than product-based) clinical registry and allow collection of long-term data from a sufficient number of patients treated with different medicinal products.

8.3.2. Patients with acute severe colitis

Patients with acute severe colitis form an important subgroup of patients with UC. The definition of acute severe colitis, which has most commonly been used, is that of Truelove &Witts. Limited amount of data for this group of patients may be acceptable for this indication, but will need to be supported by other data, (in particular safety data, but also data on efficacy in other subgroups of UC). Acute severe colitis, refractory to corticosteroids, may be defined using indices that predict colectomy in this population, e.g., the Swedish fulminant colitis index or the Oxford index. Evaluations should initially be on a daily basis. Studies should be either active controlled (standard care including high dose corticosteroids) or placebo-controlled add-on to standard care. Avoidance of colectomy short- and long-term are relevant primary endpoints in this population.

8.3.3. Patients with pouchitis

Patients with pouchitis post-colectomy with ileal pouch-anal anastomosis form an important subgroup of patients with UC. Design should be double blind, randomised and controlled. The management of pouchitis aims at reducing bacterial overgrowth and inflammation but resistance to medical therapy is reported in up to 20%. Antibiotics form the mainstay of treatment and can be used as control in studies with new medicinal products in pouchitis. For acute pouchitis (< 4 weeks), metronidazole or ciprofloxacin should be used as comparators. In chronic, antibiotic resistant pouchitis, placebo control is acceptable. The diagnosis should be confirmed by typical clinical presentation, endoscopy and histology. Efficacy in terms of symptoms as well as MH (including histological assessment) (co-primary endpoints) should be demonstrated. The 18-point Pouchitis Disease Activity Index (PDAI), combining all three aspects (symptoms, macro- and microscopic appearance of mucosa) has been used to measure disease activity and response. However, this instrument is not fully validated and there are no generally accepted definitions of response and remission. Nevertheless, the use of PDAI may be

acceptable provided that response and remission are convincingly defined and provided that clinically relevant effects in each of the main components of the score (symptoms as well as macro- and microscopic appearance of mucosa) are demonstrated.

8.3.4. Patients with extra-intestinal manifestations

Extra-intestinal manifestations occur in a subgroup of patients with UC. They can be classified into "reactive" symptoms associated with active colitis and manifestations that occur independently of the inflammation (e.g. ankylosing spondylitis, pyoderma gangrenosum and primary sclerosing cholangitis). Separate studies are not needed in this subgroup but response to treatment should be monitored in trials and analysed separately. Primary sclerosing cholangitis is a pre-malignant condition and special consideration should be given to this patient population when included in trials with new immunomodulating agents.

9. Risk management plan

Post-marketing, a risk management plan (please see Guideline on Risk Management Systems for Medicinal Products for Human Use) will normally have to be implemented in order to monitor possible long-term consequences of use of immunosuppressive and/or immunomodulating drugs, including new biologicals. Particular attention should be paid to infectious and/or malignant complications. Furthermore, adverse reactions in different sub-population should be monitored. Whether new treatments result in reduction in surgical intervention long-term is also of interest.