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

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

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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. Possible targets of estimation that define treatment effects of interest in UC are also considered.

1. Introduction (background)

UC is a chronic, relapsing inflammatory bowel disease affecting the rectum and in many instances also part of/the entire 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. In general, mortality is not increased in UC but the disease may present as life-threatening acute severe colitis.

The mainstay of therapy for mild to moderate UC is 5-aminosalicylic (5-ASA) agents. These agents are effective at inducing and 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 treatment or prevention. Intestinal continuity can be restored by construction of an ileo-anal pouch.

Pouchitis is an inflammation of the ileal pouch, occurring in up to 45% of patients with an ileo-anal pouch.

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.

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).
- ICH E9 Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96).

4. Patient selection

4.1. 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 symptoms (diarrhoea and rectal discharge of blood and/or pus), endoscopic findings (decreased/absence of vascular pattern, erythema, friability, granularity and ulcerations in colorectal mucosa), and histological findings (crypt distortion/abscess, neutrophils, 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 colon/rectum distal to the splenic flexure (E2) and 3) extensive UC (E3) involving the colon proximal to the splenic flexure (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 can be categorised according to their response to previous treatments into:

4.1.1. Refractory UC:

Patients with evidence of active inflammation despite an adequate course of treatment with a specific drug (or group of drugs) can be categorised as being refractory to that drug (or group of drugs). The exact definition of “adequate course of treatment” (i.e. dosage and duration of treatment) must be pre-specified (prior to inclusion), clearly defined and adequately justified. For corticosteroids, the definitions of refractoriness as proposed by ECCO are considered acceptable. For biologicals, this primary lack of effect is usually referred to as primary non-response.

4.1.2. Intolerance to treatment

Patients with evidence of serious side effects precluding continued treatment with a specific drug can be categorized as being intolerant to that drug (or group of drugs). The exact definition of what type of side effects preclude continued treatment must be pre-specified, clearly defined and adequately justified.

4.1.3. Dependence on treatment

Patients who respond to treatment but flare upon discontinuation may be categorized as having dependent (to that treatment) disease. The exact definition of dependence in terms of severity and timely course of flares must be pre-specified, clearly defined and adequately justified.

For corticosteroids, the definitions of dependence as proposed by ECCO are considered acceptable.

4.1.4. Secondary non-response to treatment

For biologicals, it may be relevant to distinguish between refractoriness (primary non-response, please see above) on one side and loss of response (secondary non-response) on the other side. Patients having had an initial response to the drug but subsequently losing the response is categorised as being secondary non-responders to that drug. What constitutes an initial response should be pre-specified, clearly defined and adequately justified.

4.2. 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. Assessment of efficacy

5.1. Efficacy criteria / treatment goals

The goal of treatment of ulcerative colitis is achieving and maintaining symptomatic and endoscopic remission.

The historical paradigm for the treatment of UC has been highly influenced by the limited availability of treatment options, mainly consisting of (systemic) corticosteroids and “conventional” immunosuppressants (such as AZA and MP), dividing the treatment phases into an induction and a maintenance of remission phase, owing to the well known facts that corticosteroids are acting quickly to induce remission, but are unsuitable to maintain remission in long-term treatment (and induce relevant undesirable effects), and that conventional immunosuppressants are usually not suitable to induce a fast response, but can be used to maintain remission once achieved by other means. Similarly, the paradigm has also been reflected in guidelines of learned societies which repeatedly described the aims of treatment being “induction and maintenance of remission”.

However, following the introduction of TNF-inhibitors (and more recently integrin-inhibitors) which are intended for continuous long-term treatment to induce remission and prevent relapse, the treatment paradigms have changed making the distinction between the induction and maintenance phases less relevant. Nevertheless, the distinction between induction and maintenance of remission may still be relevant for new drugs that due to e.g. either slow onset of action or long-term safety problems are only suitable for one or the other of the previously mentioned treatment phases.

5.2. 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 reported outcomes (PRO). There are a number of clinical indices, e.g. SCCAI (simple clinical colitis activity index) and Mayo Scoring Tool that mainly includes patient reported symptoms. Whereas the symptom part of the Mayo score may be used until fully validated scores are available, 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 symptoms of UC, e.g. stool frequency and rectal discharge of blood. An instrument to be used as primary outcome measure in pivotal clinical trials in UC should be 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). A significant effect on both aspects of the disease is required at a population level (co-primary endpoints). Composite indices including both symptoms and mucosal healing (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 reported sub-score and the endoscopic score is expected (co-primary endpoints). 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 faecal calprotectin are considered supportive but cannot replace direct endoscopic evaluation of inflammation.

5.3. Target of estimation (Estimand)

The scientific question(s) of interest, i.e., what the trial seeks to address and ultimately, the target(s) of estimation (estimand) should be clearly specified. Trial planning, design, conduct, analysis and interpretation must be aligned with the estimand. Please refer to ICH E9(R1) Draft Addendum on estimands and Sensitivity Analysis in Clinical Trials (EMA/CHMP/ICH/436221/2017).

The primary targets of estimation should estimate treatment effects based on the achievement (induction of remission/short term treatment) or maintenance (maintenance of remission/long term treatment) of symptomatic and endoscopic remission. In the specification of each estimand, events that may occur after treatment is initiated (called intercurrent events) and that may affect the interpretation of the variable of interest must be reflected. Relevant events to consider include treatment discontinuation (due to lack of tolerability, lack of efficacy or disease progression etc.) and changes in other medications including use of rescue medication, change in background therapy, failing to taper steroids according to the protocol-planned fixed schedule, or use of prohibited medication.

The most appropriate strategy for handling the intercurrent event "treatment discontinuation" may depend on the therapeutic intent. If the therapeutic intent is inducing remission in the short term, the effect of the treatment on endoscopic and symptomatic remission regardless of treatment discontinuation could be of primary interest (i.e. a treatment policy strategy discussed in the addendum). However, if the therapeutic intent is maintaining remission or demonstration of effect in the long-term, it is recommended that a patient who discontinues treatment prematurely is considered

as being unsuccessfully treated, particularly if the reason for discontinuation is treatment-related, because UC is a chronic disease requiring long-term treatment (i.e. the composite strategy discussed in the addendum is appropriate).

In the Ulcerative Colitis setting, where other therapies (including surgery) are available, the use of rescue medication, and in particular, the initiation of corticosteroid treatment irrespectively of such being foreseen or not in the trial protocol should also be considered as a failure of the study drug (composite strategy) independently from the therapeutic intent. If steroids that are tapered are used as background medication, a failure to taper steroids according to the protocol-planned fixed schedule can be considered as a special case of rescue therapy. However, a minor deviation from the tapering schedule does not necessarily have to be considered as an intercurrent event that should be treated as a treatment failure. It has to be pre-specified and justified what constitutes such minor deviations.

If a composite strategy for addressing treatment discontinuation or changes in other medications is appropriate, occurence of the intercurrent event is included as a component of the co-primary endpoints, considering occurrence as non-response.

For secondary objectives where the treatment effect is measured as success or failure, similar considerations apply as for the primary target of estimation. However, secondary objectives where an evaluation on a continuous scale is most appropriate, an alternative approach is required. A proposal for an appropriate strategy to address intercurrent events should be made on a case by case basis, reflecting that treatment discontinuation, at least in the long term, and use of other medications can be considered as failures of study drug. It is not generally of interest to estimate the effect if all patients had remained on treatment. However, as a treatment strategy including long-term steroid use is undesirable, the treatment effect disregarding steroid intake (or failure to taper steroids) is usually not of interest when steroid intake has a positive influence on the outcome (i.e. a treatment policy strategy should not be used).

5.4. Endpoints

5.4.1. Primary endpoint

Treatment of ulcerative colitis is aimed at inducing and maintaining both symptomatic and endoscopic remission.

Consequently, co-primary endpoints of treatment should concern:

(1) The proportion of patients with symptomatic remission, and

(2) The proportion of patients with endoscopic remission.

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 patient characteristics (e.g. severity) or time of assessment (e.g. early time point). 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 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 and thresholds used, the definition of remission should encompass cessation of rectal bleeding.

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.

5.4.2. Secondary endpoints

The following secondary endpoints should be reported

- Patients achieving both MH and symptomatic remission
- Patients achieving response. Response should be defined according to the instruments used for evaluating symptoms and endoscopic appearance.
- Patients achieving remission defined more stringently than for the primary endpoint (if a less stringent approach has been chosen for the primary endpoint) or vice-versa
- In studies where steroids are not tapered at time of evaluation of the primary endpoint (i.e. short-term induction studies as stated above),
    - proportions of patients in whom either or both symptomatic and endoscopic remission are achieved without concomitant steroid treatment
    - proportions of patients in whom either or both symptomatic and endoscopic remission are achieved at particular doses of concomitant steroid treatment (e.g. 5, 10 or 20 mg prednisolone or equivalent).
- Numerical, separate evaluations of the individual components of the symptom score, and of MH score
- Histological evaluation of mucosal inflammation, including number of patients achieving histological normalisation
- Individual patients achieving MH, judged endoscopically, as well as combined symptomatic, biomarker (=normalisation of faecal calprotectin) and histological normalisation
- Changes in stool frequency
- Laboratory measures of inflammation (e.g. faecal calprotectin)
- Time to remission (symptom scores and biomarkers only)
- Time to response (symptom scores and biomarkers only)

The following secondary endpoints may be reported

- 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)
- Reduction in number of colectomies (primarily relevant in studies of acute severe ulcerative colitis).

Additional secondary endpoints may be included if adequately justified.

6. Study design

6.1. 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).

6.2. Interactions

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

6.3. 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 treatment goal 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.

6.4. Confirmatory studies

6.4.1. Study population

Patients included in studies for the treatment of active disease 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 recent (1 month) endoscopic and histological examination. As there are currently no fully validated PROs, a score of 9-12 in 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) and symptom burden. Patients included should be well characterised especially as regards disease extent (proctitis, left-sided or extensive), duration, disease activity and smoking status. The minimum time from onset of symptoms should be at least 3 months at inclusion. Shorter duration of disease has to be justified and in this situation care must be taken to avoid inclusion of patients with diarrhoea due to other causes e.g. infections.

The patient population should also be well characterised in terms of previous treatment experience as efficacy and safety may differ in first, second and third line settings (treatment naïve, failure to standard (non-biologic) treatment and failure to biologics, respectively). The reasons for failure/discontinuation of previous therapy should be provided. The study population should match the proposed target population.

6.4.2. Design elements

6.4.2.1. Studies for a general claim of "treatment of UC"

Clinical trials in UC should be randomized, with parallel, active comparator and/or placebo treatment arms, and double-blinded. To fulfil a claim for the treatment of ulcerative colitis, it is expected that at least two confirmatory trials are provided, which could be performed in different disease stages (e.g. early ulcerative colitis who has failed standard, non-biologic treatment or patients who have failed on multiple treatments, including biologics). The choice of the disease population determines the indication. If studies (e.g. add-on design) require stable disease severity on immunosuppressants such as thiopurines, this medication should be given for at least the time required for the clinical effect to be fully established and at the clinically optimal dose prior to initiating treatment with the test drug. For all studies, the criteria for use of rescue drugs should be pre-defined. Preferably, rescue drugs are standardised. Assessment of relevant subpopulation or subgroup analyses should be prospectively planned. Preferably patients should be stratified according to previous treatment and/or background treatment.

Both, short-term and long-term efficacy should be demonstrated and therefore, two time-points have to be part of the primary evaluations (see above). Depending on the design of the trials, statistically significant effects would need to be demonstrated at both early (6-12 weeks), as well as late (6-12 months) time-points. Because mucosal healing usually takes longer than symptomatic improvement and remission, the timing of the evaluation of the endoscopic endpoints – depending also on the trial design chosen – may differ from the timing of the evaluation of the symptomatic endpoints.

For the demonstration of short-term efficacy ("induction of remission"), the duration of a study is usually 6 to 12 weeks but depends on the mode of action, magnitude and time course of effect related to the test drug. Shorter or longer study duration may be acceptable provided it is adequately justified. In all instances, the design should allow an assessment of the time to onset and maximal effect on the primary outcome.

Maintenance of efficacy should be demonstrated in long-term studies, either as an extension study of the previously mentioned short term studies maintaining blinding and randomisation (treat through design) or as a re-randomisation of responders in the previously mentioned studies to either placebo or test drug (randomised withdrawal study). In both instances, the total duration (including the short-term phase) should be at least 12 months. Whereas the treat through design is ethically problematic for placebo-controlled studies as it would subject patients to a total of 12 months of placebo, it is a viable option for active controlled studies. It may be advisable to restrict the use of placebo control for a maximum of 6 months (with adequate escape procedures at intermediate time-points) and to also include an active control for the demonstration of long-term efficacy. The comparison to the active control could be descriptive only, in case long-term placebo-controlled data in a re-randomisation design are also available, but has to show superiority, or non-inferiority to the active comparator in confirmative manner, in case such data are not available.

Re-randomisation to placebo treatment of patients having responded to an initial course of therapy causes less ethical concerns. However, the re-randomisation strategy usually requires the recruitment of a higher number of patients, due to the fact that the studies have to be powered for the final (52 week) evaluation, and the non-responders will be excluded from the re-randomisation.

6.4.2.2. Studies for an intended claim of either "Induction of remission" or "Maintenance of remission"

As indicated in Section 5, an applicant may choose only to pursue a claim of either "induction of remission" or "maintenance of remission" where this is appropriate for the mechanism of action of the new product and its anticipated safety and efficacy profiles. For a claim of induction of remission, the requirements are not different from what has been stated in the previous section (apart from the requirement of long term studies which obviously are not required). For a claim of "maintenance of remission" it needs to be demonstrated that patients being in complete remission at study entry remain in remission throughout a full 52-week study period. If also responders and not only patients in remission are included in a randomized, placebo-controlled withdrawal study, the statistical analyses would have to be powered to show efficacy for those patients being in remission at study entry to support the claim of "maintenance of remission".

6.4.3. Choice of comparator

The choice of comparator will depend on the setting 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 provide a direct comparison with current generally accepted standard 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 (if ethically justifiable, ref. ICH E10).

For a second line indication (after failure or intolerance to primary therapy), placebo is an acceptable comparator (monotherapy or add-on to established therapy) but depending on the exact target population, an active comparator may also be required. In case of add-on, the established therapy is continued as background therapy (if no intolerance to the established therapy and if some residual benefit is reasonably possible) in both arms. Failure of first line treatment should be clearly defined (please see chapter 4).

In long-term randomised withdrawal studies, aiming at demonstrating maintenance of efficacy, placebo is, as previously stated, the relevant comparator (if ethically justifiable). In this setting, an active comparator is less useful as the study population specifically is selected for a favourable response to the test drug

As mentioned above, the inclusion of active comparator into clinical trials studying long-term treatment appears to be more easily implemented in designs without re-randomisation ("treat-through").

6.4.4. Previous and concomitant treatment

Patients with UC usually receive maintenance treatment (e.g. aminosalicylates and/or thiopurines) and should in general be allowed to continue with these during a trial in active disease as background therapy. Changes in background therapy may be an intercurrent event (please see above) that can complicate the estimation of the treatment effect. 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. Dependency/refractoriness to previous treatment should be pre-specified and defined as previously mentioned. 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. Antibiotics should normally be excluded.

6.4.4.1. Concomitant steroid treatment

Patients entering early treatment phase while on steroids should either remain on a fixed dose for the duration of the short-term study (provided that this does not pose a safety risk to the patient) or preferably have their steroids tapered according to a fixed schedule. Patients who have not had their corticosteroids tapered before or within the early treatment phase should have their steroids tapered within 12 weeks after entering the maintenance phase (i.e. during the first 12 weeks of the maintenance phase). Tapering schedules should be standardised. Usually tapering can be done at a rate equivalent with 2.5 to 5 mg of prednisolone/week.

6.4.5. Statistical considerations

Choices made regarding statistical analysis, including the handling of missing data, must be aligned with the agreed target(s) of estimation (please refer to section 5.3). These must be pre-specified and fully justified in the study protocol.

It is of utmost importance that all efforts are made to collect the necessary data to align with the agreed targets of estimation. For the estimands of primary interest, where occurrence of a specific intercurrent event is considered a treatment failure (composite strategy), data for the clinical outcome variable after the intercurrent event is not needed for estimation. However, those data might still be required for estimation of estimands reflecting other scientific questions of interest, e.g. if it is of interest to estimate the treatment effect on symptoms measured as a continuous variable, using the treatment-policy strategy to reflect use of additional medication.

It is also important to differentiate between intercurrent events and missing data. In particular, refusal to undergo repeated endoscopy might play a role, especially in trials in which endoscopy will be undertaken up to 3 times within a year. However, while refusal of endoscopy results in missing data irrespective of the definition of the estimand, it is not an intercurrent event and missing data for these patients needs to be handled in the statistical analysis, in accordance with the target of estimation. For example, even if treatment discontinuation is to be considered as non-response, missing data for patients who are still on treatment but did not undergo endoscopy should still be imputed, for example using multiple imputation based on remission probability of patients still on treatment (possibly taking additional covariates into account).

For a general claim “treatment of UC”, short as well as long-term efficacy should be demonstrated. Thus, assessment of short- and long-term efficacy are considered co-primary and no adjustment for multiplicity is nessary. In case a study is intended to demonstrate either induction OR maintenance of remission, a multiplicity issue may arise and should be addressed.

7. Safety aspects

7.1. Specific effects

Identified adverse events should be characterised in relation to the duration of treatment, the dosage, 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.

7.2. 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, it should be investigated 1) if binding-antibodies and/or neutralising antibodies against these products develop during treatment and 2) if these antibodies have an impact on the long-term efficacy and safety of the product. Concomitant use of immunosuppressants in add-on studies may increase the risk for serious adverse events, including opportunistic infections and malignancies and decrease the ability to detect immunogenicity. 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. This should be considered as part of post marketing commitments.

7.3. Studies in special populations

7.3.1. 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.

Given the long-term nature of treatment and the importance of adherence to treatment plans, there is a need to develop age-appropriate formulations for children and to demonstrate their acceptability in studies. In this regard, please to refer to the EMA paediatric formulation development guideline (EMA/CHMP/QWP/805880/2012 Rev. 2) in section 3.

7.3.1.1. 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. It is emphasised that obtaining PK data in all age groups is prerequisite for this purpose. The results of this covariate analysis can be used in case a certain exposure (AUC or C_{trough}) for instance from adults is aimed for, to identify whether different mg/kg doses per age group may be needed to reach the same exposure across the entire paediatric age range.

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.

7.3.1.2. Efficacy in paediatric patients

The aim of UC treatment in children should be achieving remission without affecting growth and maturation. Remission should be defined as symptomatic remission accompanied by endoscopic MH. Symptomatic remission and endoscopic MH should be used as co-primary endpoints. Symptomatic response alone is not considered acceptable in children, based on the fact that UC is a chronic disease with potential serious consequences. In studies, representative changes in mucosal appearance are expected to be evaluated by endoscopy. 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 currently not available, for the time being, the use of the PUCAI as a surrogate for symptomatic remission is considered acceptable. Symptomatic 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 symptomatic 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.

7.3.1.2.1. Strategy and design

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 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 beset 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 consequently a treat-through design (see relevant adult section) will be acceptable. In addition 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. Dose-finding aspects in long-term treatment should be addressed.

7.3.1.3. 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 (e.g. while patients are on chronic therapy / 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 a 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.

7.3.1.4. Extrapolation of data

Based on some similarity of the disease in adults and in children in terms of overall disease pathology and progression and possible treatment targets, extrapolation of efficacy and/or safety should be considered in order to spare children from unnecessary trials.

Application of extrapolation approaches 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.

7.3.2. 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 in steroid refractory acute, severe ulcerative colitis should be active controlled (cyclosporine or infliximab). For studies in patients not being refractory to steroids, steroids should be the comparator of choice. Avoidance of colectomy short- and long-term are relevant primary endpoints in this population.

7.3.3. Patients with pouchitis

Patients with pouchitis (following 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.

7.3.4. 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.

7.3.5. Elderly patients

It should be ensured that adequate number of elderly patients are included in clinical trials, since clinical effects in these patients may be influenced by factors such as reduced glomerular filtration rates, increased susceptibility to adverse events (e.g. delirium, fractures), and drug-drug interactions in case of polypharmacy. Please see ICH E7 guideline for additional guidance.

8. Risk management plan

A risk management plan 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.