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Guideline on the development of new medicinal products for the treatment of Crohn's Disease

Draft

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This guideline replaces "guideline on the development of new medicinal products for the treatment of Crohn's Disease (CPMP/EWP/2284/99 Rev. 1).

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

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30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Guideline on the development of new medicinal products for the treatment of Crohn's Disease

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Executive summary

This is the 2nd revision of the Guideline on the development of new medicinal products for the treatment of CD.

The main aim of this 2nd revision was 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)

CD is a chronic relapsing, remitting inflammatory disease of the gastrointestinal tract, the cause of which remains unknown. Some patients may have a continuously clinically active disease. The disease affects the gastrointestinal tract discontinuously from mouth to anus, but most commonly the disease is located both in ileum and colon (40%), followed by a disease in the small bowel only (30%), and in the colon only (25%). It occurs in all ages with a higher incidence in the younger population and there is no marked sex difference. The incidence of CD in European countries is estimated to be 6-8.5/100.000. Recent epidemiological studies have found increased mortality risk in patients with CD and most individuals experience an impact of the disease on their daily life.

In the absence of specific markers or aetiological mechanisms, a diagnosis is usually based on composite clinical and pathological features and the exclusion of alternative disease states. CD has been classified by disease phenotype into primarily inflammatory disease, stricturing disease or fistulising disease modified by the presence of upper gastrointestinal or perianal disease (Montreal classification 2005). Over the course of the disease, phenotype commonly changes from predominantly inflammatory disease to stricturing disease.

The symptoms are partly determined by the anatomical location and the severity of the disease and there may be no direct correlation between an individual's symptoms and endoscopic and radiological findings. The major signs and symptoms are diarrhoea, abdominal pain and weight loss. Physical findings reflect the site and severity of the pathology. Abdominal tenderness or presence of an abdominal mass reflects serosal inflammation or abscess formation. Perianal manifestations are common. Extraintestinal manifestations include ocular inflammation, arthropathies, skin lesions and a spectrum of hepatic diseases. Due to their transmural nature, inflammatory lesions can result in the formation of strictures and fistulae, which can lead respectively to obstruction and abscesses.

Medical therapy recommended by clinical guidelines includes antibiotics (for colonic disease), corticosteroids, immunosuppressant drugs and biologics (anti-tumour necrosis factor (TNF) α agents and adhesion molecule inhibitors). Nutritional support also has a role as primary therapy or as adjunct to other treatment. When medical treatment is unsuccessful or with certain complications, surgery is indicated. More than 70% of patients with ileal disease will require surgery at least once during the course of their disease. Due to therapeutic failures and serious side effects of present therapies, alternatives are needed.

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 CD. This document is aimed to replace the

'Guideline on the development of medicinal products for the treatment of CD' (CPMP/EWP/2284/99 rev 1). Guidance is provided on strategy and design of clinical studies as well as on long term safety and post marketing follow up. 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)
- EMA/199678/2016Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005).

4. Criteria and Standards for Patient selection

Definition and specifications of the disease

Active CD

The majority of patients experiences periods of active disease**, which is defined by clinical signs and symptoms,** as well as **signs of mucosal inflammation**.

Thus, in addition to signs and symptoms of active disease, patients included in clinical trials aiming at demonstrating efficacy in this situation should have evidence of active mucosal inflammation documented by recent endoscopy (ileocolonic disease) and/or imaging of the small intestine (e.g. magnetic resonance enterography (MRE)/capsule endoscopy) (small intestinal disease only). Adjudication of endoscopic/image 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. Histological evaluation of activity prior to inclusion is encouraged. The use of biomarkers of inflammation (C-reactive protein (CRP), faecal calprotectin) is encouraged but currently available biomarkers cannot provide stand-alone evidence of inflammation.

Patients with evidence of active inflammation over a period of three to six months despite treatment can be divided into 2 categories.

- **Steroid dependent CD:** Patients who respond to steroids but whose disease flares on tapering (precluding steroid withdrawal) are classified as being steroid dependent. Precise criteria for minimum duration of treatment and dose should be pre-specified and justified with reference to national and international consensus documents. For example according to the European Crohn's and Colitis Organisation (ECCO) guideline patients

- unable to reduce steroids below the equivalent of prednisolone 10 mg/day (or budesonide below 3 mg/day) within 3 months of starting steroids, without recurrent active disease, or
- who have a relapse within 3 months of stopping steroids

are classified as steroid dependent.

The use of corticosteroids at baseline does not automatically mean steroid-dependency, unless previous attempts to taper steroid use have proved unsuccessful. Tapering schedules must be standardised and too rapid tapering avoided.

- **Refractory CD:** Patients who have active disease despite the use of corticosteroids/immunosuppressants in an adequate dose and for an adequate time period are defined as being steroid refractory/immunosuppressant refractory. The precise dose and duration should be pre-specified and justified with reference to consensus documents. For example according to the ECCO guideline, patients who have active disease despite prednisolone of up to 0.75 mg/kg/day over a period of 4 weeks. Patients are refractory to azathioprine/6-mercaptopurine if they do not respond to a sufficient dose within 3 to 6 months. Patients are refractory to anti-TNF therapy if they make no initial response to appropriate doses/duration of anti-TNF therapy. The exact definition should be based on the dose/duration of the approved labelling.

CD 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 determined by endoscopy/MRE) who have no or very mild symptoms are considered in remission. Precise definition depends on the instruments used to assess mucosal inflammation and symptoms (please see below). Remission can be achieved either by medical treatment or surgery.

5. Possible indications/treatment goals

In order to obtain an indication for “treatment of active Crohn’s disease”, efficacy in both ”induction of remission” as well as “”maintenance of remission” should be demonstrated.;

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.

An indication of ”Treatment of fistulising CD” may also be claimed provided that efficacy has been adequately demonstrated..

Other claims such treatment of abscess, treatment of obstruction 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 CD is steroid-free clinical and endoscopic remission.

6. Assessment of efficacy

6.1. Methods to assess efficacy criteria

A new drug intended for the treatment of CD is expected to provide symptomatic relief to the patient based on a documented effect on the inflammatory 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.

While Crohn's Disease Activity Index (CDAI), combining both patient reported data and surrogate markers of inflammation, has previously been used extensively in clinical trials in CD, both reliability and validity of this index has been questioned. The reproducibility of the CDAI may be limited, as significant inter-observer variability even in the hands of experienced clinicians has been observed. Furthermore, many of the components of the CDAI are subject to interpretation and may be biased. Consequently, the use of this index as a primary endpoint for future studies is discouraged.

Instead of a combined index such as CDAI, signs and symptoms and inflammation should be evaluated independently. A significant effect on both aspects of the disease is required (co primary endpoints). Symptomatic relief should be evaluated by patient related outcomes (PRO) (e.g. number of lose stools and abdominal pain). This guideline therefore recommends the further development and validation of PRO instruments for the use as primary outcome parameter in clinical trials in CD. Such an instrument should include the clinically important signs and symptoms of CD,. e.g. abdominal pain and diarrhoea. An instrument to be used as primary outcome measure in pivotal clinical trials in CD should be completely and rigorously validated. For instruments including two or more parameters it is expected that response definition include response in terms of all parameters.

Mucosal inflammation should be evaluated by endoscopy and/or imaging studies (e.g. MRE). The grade of mucosal inflammation should be evaluated by a validated scale, e.g. CDEIS (CD Endoscopic Index of Severity) or SES-CD (Simple Endoscopic Score for CD). Surrogate markers of inflammation, such as CRP and faecal calprotectin are considered supporting but cannot replace direct evaluation of inflammation.

6.1.1. General Aspects

Primary endpoint

Achieving/maintaining symptomatic remission free of steroids is an appropriate primary endpoint. In patients receiving systemic steroids, these should be tapered according to predefined schedules.

Remission should be defined and justified according to the instrument used for evaluating. E.g., when evaluated by a 5-point scale, symptomatic remission can be defined as "no" or "mild" symptoms. However as previously noted, achieving/maintaining MH should also be considered a primary end-point. As for the symptomatic endpoint, remission should be defined and justified according to the instrument used for evaluating. E.g. when evaluated by CDEIS, a score 0 can be used for defining remission in terms of mucosal inflammation. As outlined above, symptomatic remission and MH should be considered co-primary endpoints. However, as listed below, achieving both symptomatic remission and MH (for the individual patient) is considered an important secondary endpoint. The timing of measuring the two co-primary endpoints depends on the aim of the treatment (please see below) as well as the pharmacodynamic properties of the test drug.

In patients receiving systemic steroids these should be tapered according to predefined schedules. For induction studies of short duration requiring early evaluation of efficacy a low dose of steroids may be acceptable provided that the dose is clearly justified and pre-specified.

Secondary endpoints

- Individual patients achieving both MH and symptomatic remission
- Remission defined slightly differently from the primary endpoint (e.g. use the more stringent approach, if a less stringent approach has been chosen for the primary endpoint or vice-versa)
- Numerical evaluation of individual symptoms scales and of mucosal inflammation
- Alternative definition of remission based on the primary endpoint with the additional requirement of normalisation of CRP and/or calprotectin as well as histological normalization
- Histological evaluation of mucosal inflammation, including number of patients achieving histological normalisation
- Response, which should be defined according to the instruments used for evaluating symptoms and inflammation, respectively. E.g. a decrease in CDEIS of >5 points combined with a decrease of >2 points on a 5 point scale evaluating symptoms
- Time to remission;
- Time to response;
- Laboratory measures of inflammation (e.g. CRP, faecal calprotectin);
- Validated QoL measurement, e.g., inflammatory bowel disease questionnaire (IBDQ);
- Steroid sparing effect such as: Proportion in steroid-free remission;
- Reduction in surgical procedures.

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 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 existing 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. Exploratory studies

For the dose response ICH E4 guidance Dose-Response Information to Support Drug Registration should be adhered to. 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 the pharmacodynamic properties, safety profile, mode and speed of onset 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 CD 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 (please see Guideline on missing data). 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 an 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, active treatment should continue for 8 weeks. However, based on the mode and speed of onset of action of the new compound a shorter/longer duration may be justified. However in order to provide a useful intervention for acute active disease, symptom control is expected within 12 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 in steroid-free remission should be distinguished from those in remission whilst continuing steroids. Maintaining 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

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 and/or radiologic imaging studies (MRE is only suitable for small intestinal disease that cannot be evaluated by colonoscopy) and histological examination. The site of the disease and associated complications must be recorded. Except for steroid-dependent patients, patients should preferably be off steroid when entering studies. In patients receiving steroids at entry, the medication should be tapered before evaluation of efficacy.

As there are currently no fully validated PROs inclusion criteria based on signs and symptoms may use the CDAI score (e.g. at least 220) or the “PRO2” (e.g. of at least 14) until a validated scale is available, but patients included must also have a certain minimal level of mucosal inflammation (e.g. a score >8 when using CDEIS or a score >6 when using SES-CD). The choice of study population should reflect the proposed indication. Patients included should be well characterised especially as regards disease phenotype (inflammatory/stricturing/fistulising), duration, disease activity, complications, localisation, 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 infectious diarrhoea.

7.2.2.1.3. Choice of endpoints

Please refer to “General Aspects” above.

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 CD, it is necessary to demonstrate that the drug has either the same or an improved risk/benefit profile as the standard of care, which currently in the majority of cases includes glucocorticosteroids. 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. A third arm (a TNF-inhibitor) may provide useful information. For a second-line indication in patients with insufficient response to established therapy, it is advised that the established therapy is continued in the control arm as background therapy while in the experimental arm, established therapy (add-on) or placebo may be used in combination with the experimental agent. Failure of first line treatment should be clearly defined. In that respect, having previously been exposed (without documentation of the insufficient response) to one or more first line drug is not considered sufficient.

For patients with severe, steroid and immunosuppressive refractory CD, a comparison with an anti-TNF compound is recommended.

7.2.2.2. Maintenance of remission / Prevention of relapse

7.2.2.2.1. Design elements

The absolute 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

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 remission (as defined above) and off steroids may be included into the trials. Thus for inclusion into maintenance studies patients are expected to have MH (e.g. SES-CD, CDAIS of 0) and clinical remission (for signs and symptoms). MH should be documented by visualisation of the gastrointestinal (GI) tract by e.g., MRE and/or endoscopic examination. Patients with surgically induced remission can be entered directly and within one month after surgery and should preferably be studied in separate studies.

Trials combining induction treatment and maintenance treatment should preferably only enter patients that have achieved remission (in either the trial drug or comparator group), into the maintenance phase. Inclusion of responders is acceptable as it may yield important information on the potential benefit of continued treatment in this population. However, 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 the maintenance of steroid-free remission 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. For surgically induced remission, the primary endpoint could also be clinical post-operative recurrence. 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 evaluated.

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 and/or MRE (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 6-mercaptopurine (MP)) or TNF-inhibitors as comparators are recommended.

7.2.2.3. Treatment of fistulising CD

Treatment of acute suppurative fistulas includes surgical drainage in combination with antibiotic treatment and therefore this guideline only concerns clinical trials in patients with chronic, non-suppurative fistulas. The therapeutic goals of management of fistulising CD are to close fistulas and maintain their closure, to reduce the incidence of infections in persisting fistulas, and to limit the need for surgical interventions. Clinical studies in fistulising CD should reflect this. The primary endpoint should be complete closure of fistulas and maintenance of a closed fistula without development of new fistulas. The healing of fistula should be demonstrated by using imaging techniques. Currently magnetic resonance imaging (MRI) is the recommended technique to demonstrate internal as well as external healing of fistulas. Reading of MRI images should be blinded and preferably done centrally.

Clinical assessment of drainage, however, is an important secondary endpoint as well as changes in the perianal disease activity index (PDAI) and reduction in surgical intervention. Symptom severity, endoscopic appearance of the rectum, number and localisation, as well as complexity, of fistulas should also be registered baseline. For a first line indication, comparison should be made with standard treatment, i.e. antibiotics (metronidazole/ciprofloxacin). For the refractory population, comparison with immunomodulators and/or anti-TNF therapy is recommended. For an add-on indication, placebo is an acceptable comparator. Duration of short-term trials should be at least 12 weeks with evaluation of the primary endpoint at 8-12 weeks. For maintenance treatment, a study-duration of 12 months is recommended. For both short-term and maintenance trials, at least 12 weeks of follow-up without treatment should be included to study maintenance of closure.

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 CD 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 CD 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 CD, 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. Paediatric patients

CD 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 characterized by a more complicated disease course with higher inflammatory activity and higher need for corticosteroids and immunosuppressive therapy. Subsequently children have a higher cancer risk, longer duration of disease, severity or extension of disease compared with adult-onset IBD.

CD 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 CD 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.

In paediatric patients, exclusive enteral nutrition (EEN) is considered as effective treatment in induction of remission in children with newly diagnosed Crohn disease. EEN treatment should be considered as a comparator in trials designed for the products for first-line therapy.

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 CD
- 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 the 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 C_{trough}) for instance similar to 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 adjustments in case of sub-target trough or AUC levels in non-responders should be made based on the results obtained during the 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.

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

Endoscopic MH and disease activity scores (similar to adults) should be used as co-primary end points in clinical studies. Paediatric patient reported outcomes (pPRO) should be used as co-primary endpoint (instead of activity scores) as soon as a validated tool is available.

Currently most used clinical indexes - the Paediatric CD Activity Index (PCDAI) and its modifications (e.g. wPCDAI) are not optimal for study purpose and the use of this index as the only primary endpoint for future studies is not recommended. However, until a fully validated pPRO is available, it may serve as a surrogate for symptomatic evaluation (and the evaluation of clinical remission).

It also contains the parameter of growth velocity, which would have to be evaluated separately, if a validated pPRO is finally used. Improved growth pattern, height velocity beyond six months or finally normalised growth remains an important secondary endpoint in children.

Magnetic resonance enterography (MRE) for the evaluation of disease manifestation is encouraged as a secondary endpoint. MRE is preferable to computed tomography enterography (CTE) in children due to considerable X-ray exposure of CTE.

Extra-intestinal manifestations are more common in the paediatric population and response with regard to these is an important secondary endpoint as well.

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 CD 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-

authorization 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.

9. Risk management plan

Post-marketing, 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.