



**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**GUIDELINE ON THE DEVELOPMENT OF NEW MEDICINAL PRODUCTS FOR THE
TREATMENT OF CROHN'S DISEASE**

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EXECUTIVE SUMMARY

This Guideline intends to address the EU regulatory position on the main topics of the clinical development of new medicinal products in the treatment of patients with Crohn's disease (CD) and it replaces the document "Points to Consider on clinical investigation of medicinal products for the management of Crohn's disease" (CPMP/EWP/2284/99). Guidance is provided with respect to the design of confirmatory studies in patients with active disease where the aim should be induction of remission and in patients in remission where the aim should be to maintain steroid-free remission for at least 12 months. In addition guidance is provided about the design of studies in patients with fistulising disease where the objective should be sustained healing of fistula.

Crohn's disease activity index (CDAI) and the paediatric counterpart (PCDAI) are accepted outcome measures where a score of < 150 and < 10, respectively, defines "remission".

For compounds where long-term safety is a concern and where therefore the primary target population for treatment in clinical practice is restricted to patients with severe CD, it is advised that patients with CDAI score of at least 250, and preferably higher, are enrolled in clinical studies.

In studies designed to show activity in patients resistant to ongoing therapy and due to the relapsing – remitting nature of the disease, background therapy (+ placebo) should normally be used as reference therapy. In patients with severe, steroid and immunosuppressive refractory disease it is recommended that an anti-TNF compound is used as active reference unless otherwise justified.

1 INTRODUCTION

Crohn's disease 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 Crohn's disease 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. Crohn's disease 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 (Rome or Vienna classification modified in Montreal 2006). 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 symptoms are diarrhoea, abdominal pain and weight loss. Physical findings reflect the site and severity of the pathology. Abdominal tenderness, 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 used in clinical practice includes 5-aminosalicylic acid (5-ASA) and antibiotics (for colonic disease), corticosteroids, immunosuppressant drugs and anti-TNF α agents. 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.

While the principles used for the evaluation of medicinal products with respect to quality, pharmacology, toxicology, and pharmacokinetics will apply to these products the evaluation of efficacy must take into account the varying forms of Crohn's disease.

2 SCOPE

This Guideline intends to address the EU regulatory position on the main topics of the clinical development of new medicinal products in the treatment of patients with Crohn's disease and it replaces the document 'Points to Consider on clinical investigation of medicinal products for the management of Crohn's disease' (CPMP/EWP/2284/99). Guidance is provided on the performance of confirmatory studies (generic drug development is not covered). Any deviation from guidelines should be justified.

3 LEGAL BASIS

This Guideline should be read in conjunction with Directive 2001/83/EC, as amended. All other pertinent elements outlined in current and future EU and ICH guidelines and regulations should also be taken into account, especially those on:

- Note for Guidance on General Considerations for Clinical Trials (CPMP/ICH/291/95);
- Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95);
- Note for Guidance on Dose Response Information to support Drug Registration (CPMP/ICH/378/95);
- Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96);
- Note for Guidance on Choice of Control Group in Clinical Trials (CPMP/ICH/364/96);
- Note for Guidance on Population Exposure: The Extent of Population Exposure to assess Clinical Safety (CHMP/ICH/375/95);
- 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 Choice of the Non-Inferiority Margin (CHMP/EWP/2158/99);
- Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99);
- Guideline on Conduct of Pharmacovigilance for Medicines used by the Paediatric Population (CHMP/PhVWP/235910/05);
- Guideline on Risk Management Systems for Medicinal Products for Human Use (EMA/CHMP/96268/2005).

4 DEVELOPMENT OF NEW MEDICINALS PRODUCTS FOR THE TREATMENT OF CROHN'S DISEASE

4.1 Disease stages and potential claims

4.1.1 Patients' characteristics

Active Crohn's disease: The majority of patients experiences periods of active disease which is defined by clinical activity indices, often corroborated by biological criteria such as C-reactive protein (CRP) elevation and/or other laboratory markers, and for which the management usually includes a short course of steroids (prednisone, prednisolone or budesonide).

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

- **Steroid dependent Crohn's disease:** Patients who respond to steroids but who's 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. The use of corticosteroids at baseline is not equal to steroid-dependency, unless previous attempts to taper steroid use have proved unsuccessful. Tapering schedules must be standardised and too rapid tapering avoided.
- **Refractory Crohn's disease:** Patients who have active disease despite the use of corticosteroids in an adequate dose and for an adequate time period are defined as being steroid refractory. The precise dose and duration should be pre-specified and justified with reference to consensus documents. 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-tumour necrosis factor (TNF) therapy if they make no initial response to two appropriate doses of anti-TNF therapy.

Crohn's disease in remission: Patients with a CDAI score of < 150 are considered in remission. Remission can be achieved either by medical treatment or surgery.

4.1.2 Potential claims

The principal aims of management of Crohn's disease and thus, potential indications are:

- Treatment of active disease / Induction of remission;
- Maintenance of remission / Prevention of relapse;
- Treatment of fistulising Crohn's disease.

Other claims such as steroid sparing, treatment of abscess, endoscopic remission, treatment of obstruction and improvement in quality of life should not form a part of the indication, but may be included in other relevant section(s) of the prescribing information.

4.2 Efficacy

4.2.1 Treatment of active disease/Induction of remission

Patients to be included

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. It is recommended that patients included in the trials should have active disease as determined by a CDAI score of at least 220. Depending on the place of the drug in the therapeutic arsenal, a CDAI score of at least 250 may be appropriate in some cases. Consideration should be given to reducing heterogeneity of disease characteristics in the patient population.

Failed prior therapies and ongoing treatment should also be taken into account.

Study design

In active Crohn's disease the design should be a randomised double blind parallel group comparison. It is recommended that diagnosis and extent of Crohn's disease is sufficiently documented by recent visualisation of the gastrointestinal tract, by e.g. radiology, endoscopic examination (including capsule endoscopy) and histological examination. The site of the disease and associated complications must be recorded.

Treatment under double-blind conditions should continue until the completion of the active treatment period in the absence of clinical deterioration or failure to improve according to pre-defined definitions for treatment failures. In all cases patients should complete the pre-specified follow-up

period for the study. Escape procedures for non-responders should be included in the protocol, which should secure a meaningful comparison of the treatments.

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.

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 Crohn's disease, it is necessary to demonstrate that the drug has either the same or an improved risk/benefit profile as the standard of care, which currently in the majority of cases includes glucocorticosteroids. 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, the trial should (when ethically justifiable) also include a placebo arm to provide internal validation of the study.

In order to support an indication for add-on to established therapy, the drug should be compared with add-on placebo. For a second-line indication in patients with insufficient response to established therapy, it is advised that the established therapy is continued in the control arm as background therapy while in the experimental arm, established therapy or placebo may be used in combination with the experimental agent.

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

Response variables

The outcome variables for active disease may include a symptom, sign or composite index of symptoms and signs; endoscopic or radiological manifestations; histological changes or, laboratory indicators of acute inflammation and quality of life assessment (QoL). An ideal measurement of the activity of Crohn's disease does not exist, but CDAI is the best that is currently available. CDAI scores of 150-219 define a mildly active disease, between 220-450 define a moderately active disease and scores > 450 define severely active disease. Remission is defined by reduction in CDAI score to less than 150, which is maintained for at least two weeks. A patient is called a responder, if remission has been achieved or a reduction of at least 100 in CDAI has been observed at the end of the treatment period.

Primary endpoint

The proportion of patients achieving remission within the period of about four to eight weeks, based on the pharmacodynamic properties of the test drug, is an appropriate primary end-point to justify short-term treatment of active Crohn's disease.

Secondary endpoints

- Proportion of responders (response defined as above);
- Time to remission;
- Time to response;
- Laboratory measures of inflammation;
- Validated QoL measurement, e.g., inflammatory bowel disease questionnaire (IBDQ);
- Assessment of endoscopic healing, e.g., Crohn's disease endoscopic index of severity (CDEIS);
- Mean or relative change in CDAI score;
- Steroid sparing effect such as: Proportion in steroid-free remission;
- Reduction in surgical procedures.

In patients who are steroid dependent, withdrawal of the steroids may be the objective. The primary endpoint should be the number of patients in whom steroids could be withdrawn and who maintained a CDAI of less than 150 for at least six months after withdrawal. Procedures for withdrawal (e.g., tapering schedules) should be predefined.

It is recommended to stratify patients according to disease activity. The response with regard to intestinal and extraintestinal 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.

Study duration

Active treatment should continue for at least eight weeks or for at least 2 cycles of therapy depending on which is the longer. 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.

4.2.2 Maintenance of remission/Prevention of relapse

Patients to be included

Patients who are in remission for at least one month may be included into the trials. In all cases, it is recommended that the diagnosis and extent of CD be documented by recent (within approximately 18 months) visualisation of the gastrointestinal (GI) tract by e.g., radiology, endoscopic examination and histological examination. The site of disease and associated complications must be defined. 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. If only remitters to the trial drug are allowed to enter the maintenance phase of the study, this will be reflected in the labelling. A re-randomisation is recommended. Without re-randomisation interpreting results from combination trials is problematic as results from the induction phase will influence the final results of the maintenance phase. For combined studies, it is required that statistically and clinically significant results are obtained for both phases of the trial.

Study design

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.

Treatment under double-blind conditions should continue until the completion of the study period in the absence of clinical deterioration according to pre-defined definitions for treatment failures.

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 (6-MP) or other immunomodulators are recommended.

Response variables

It is recommended that the primary end-point should be the proportion of patients in whom steroid-free remission is maintained without surgery throughout at least 12 months. 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 considered. Endoscopic recurrence per se is only acceptable as a secondary endpoint.

Study duration

The treatment period should be aimed at a minimum of 12 months. A follow-up period of 3 months after treatment discontinuation should be included in the trial.

4.2.3 Treatment of fistulising Crohn's disease

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 Crohn's disease 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 Crohn's disease 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. Changes in CDAI score are of secondary interest but typically patients with fistulising Crohn's disease have low CDAI scores. CDAI score, however, should be documented at baseline and for new anti-inflammatory drugs it is recommended that CDAI is used as a stratification variable (absence or presence of active inflammation). 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.

4.3 Studies in special populations

Children and adolescents

As Crohn's disease occurs in a relatively young population, often diagnosed during childhood and adolescence, separate studies in these patients are encouraged, both in active inflammatory disease as well as in fistulising disease. Due to the unknown risk of the combined use of immunosuppressive therapy and newer biological treatments in children, monotherapy studies are encouraged, if ethically justifiable. Optimal dosing needs to be determined and effects of treatment on growth can only be evaluated in paediatric trials. The diagnosis of Crohn's disease in children should be made on the basis of examinations, including ileocolonoscopy and histology. Type of disease, severity, localisation and extent of the disease should be documented. The aims of treatment in paediatric studies are essentially the same as for adults. Treatment of Crohn's disease in children is less well established, but in clinical practice the same drugs as in adults are used and thus in clinical trials, comparators should be the same as for adult studies. In addition, nutrition therapy can be considered for comparison.

For measurement of efficacy, it is recommended to use the paediatric CDAI score (PCDAI). The PCDAI score is a validated multi-item measure of severity of illness that, compared to the adult-

derived CDAI, includes linear growth and places less emphasis on subjectively reported symptoms and more on laboratory parameters of intestinal inflammation. The PCDAI score ranges from 0 to 100 where scores < 10 reflects inactive disease, 10-30 mild disease and scores > 30 moderate to severe disease. The clinically meaningful decrease to define response is unknown, even though a decrease of 15 points has been used. Primary endpoint should be steroid-free remission. In long-term trials, assessment of growth using validated methods must be included among the endpoints. Resume of normal growth velocity and reach of age-corrected height should be assessed over 12 months. Use of dual-energy X-ray absorptiometry (DEXA) is recommended to evaluate body composition. For measurement of quality of life, scales validated for use in children should be used.

Safety and especially long-term safety is crucial in this population. Little is known about the potential risks of new immunomodulators on maturation and growth and monitoring of these parameters is mandatory in long-term trials with these agents. Especially in children withdrawal studies may be appropriate to minimise the exposure.

4.4 Safety

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 Crohn's disease 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 Crohn's disease affects young women of childbearing potential, special attention is warranted in this population.

4.4.1 Long-term safety

Given the potentially long-term use of drug therapy in Crohn's disease, 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.

4.4.2 Post-marketing

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.

ABBREVIATIONS

- 5-ASA: 5- Aminosalicylic Acid
- 6-MP: 6- Mercaptopurine
- Anti-TNF Therapy: Anti-Tumour Necrosis Factor Therapy
- CD: Crohn's Disease
- CDAI: Crohn's Disease Activity Index
- CDEIS: Crohn's Disease Endoscopic Index of Severity
- CRP: C-Reactive Protein
- DEXA: Dual-energy X-Ray Absorptiometry

- IBDQ: Inflammatory Bowel Disease Questionnaire
- MRI: Magnetic Resonance Imaging
- PCDAI: Paediatric Crohn's Disease Activity Index
- PDAI: Perianal Disease Activity Index
- QoL: Quality of Life Assessment

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