Committee for Medicinal Products for Human Use (CHMP)

Draft

Guideline on the Development of New Medicinal Products for the Treatment of Crohn’s Disease

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The proposed guideline will replace the current Points to consider on clinical investigation of medicinal products in the management of Crohn’s disease (CPMP/EWP/2284/99)

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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. It should be read in conjunction with Directive 2001/83/EC, and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations, 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)
- 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)

1. INTRODUCTION
Crohn’s disease is a chronic relapsing, remitting inflammatory disease of the gastrointestinal tract, the cause of which remains unknown. 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 a relatively young 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. Whether mortality is increased in patients with Crohn’s disease is currently debated, however, 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, strictureing disease or fistulising disease (Rome or Vienna classification modified in Montreal 2006).

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 reflect serosal inflammation. 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 includes corticosteroids, antibiotics, immunosuppressant drugs and anti-TNFα agents. When medical treatment is unsuccessful or with certain complications, surgery is indicated. More than 70% of patients 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


3. DISEASE STAGES AND POTENTIAL CLAIMS

3.1 Disease stages to be studied

**Active Crohn’s disease:** The majority of patients experience periods of active disease for which the management usually includes a short course of steroids (prednisolone or budesonide). Patients showing signs and symptoms with evidence of active inflammation well defined by biological criteria (CRP, ESR) 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 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. Merely the use of corticosteroids at baseline is not equal to steroid-dependency.

- **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.

**Crohn’s disease in remission:** Patients with a CDAI score of < 150 (see 2.2.1.4) are considered in remission. Remission can be achieved either by medical treatment or surgery.

3.2 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.

4. EFFICACY

4.1 Treatment of active disease/Induction of remission

4.1.1 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. Depending on the aim of the treatment, it is recommended that patients included in the trials should have active disease as determined by a CDAI score of at least 220. Dependent on the place of drug in the therapeutic arsenal a CDAI score of at least 250 may be appropriate in some cases.
4.1.2 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 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 study period in the absence of clinical deterioration or failure to improve according to pre-defined definitions for treatment failures. In all cases follow-up should continue until the planned end of the study. Escape procedures for non-responders should be included in the protocol, which should secure a meaningful comparison of the treatments.

4.1.3 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 new drug is at least as effective and safe 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 + placebo versus the experimental compound plus continued background or placebo as monotherapy.

4.1.4 Response Variables

The variables of response 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 the Crohn’s disease activity index (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 eight weeks 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
- Individual items of the CDAI.
- 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

In patients who are steroid dependent, withdrawal/decrease 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 localisation and 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. Consideration should be taken for the experimental drug and the comparator regarding efficacy of the target organs e.g. mode of delivery into the intestines for locally acting drugs.

4.1.5 Study duration

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

4.2 Maintenance of remission/Prevention of relapse

4.2.1 Patients to be included

Patients who are in remission as defined by a CDAI of < 150 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 12 months) visualisation of the 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 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 and preferably a re-randomisation should be done. If only remitters to the trial drug are allowed to enter the maintenance phase of the study, this will be reflected in the labelling. For combined studies, it is required that statistically and clinically significant results are obtained for both phases of the trial.

4.2.2 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 should receive placebo or test drug as add-on therapy.

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.

4.2.3 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-MP or other immunomodulators are recommended.

4.2.4 Response variables

It is recommended that the primary end-point should be the proportion of patients in whom remission is maintained (i.e. CDAI <150) and no surgery needed throughout at least 12 months. For surgically induced remission, the primary endpoint could also be clinical post-operative recurrence. Endoscopic recurrence in this population is only acceptable as a secondary endpoint.

4.2.5 Study duration

The treatment period should be aimed at a minimum of 12 months. A follow-up period of three months after treatment discontinuation should be included in the trial.
4.3 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 (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 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 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 both short-term and maintenance trials, at least 12 weeks of follow-up without treatment should be included to study maintenance of closure.

5. 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 done 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 established compared with treatment in adults but in clinical practice same drugs that are used and thus for comparison in clinical trials, comparators should be the same as for adult studies but 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. Primary endpoint should be 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.
6. 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.

6.1 Long-term safety

Given the potentially long-term use of an established 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 and 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.

6.2 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.