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3 Committee for Medicinal Products for Human Use (CHMP)

4 Concept paper on the revision of the guideline on the 5 development of new medicinal products for the treatment 6 of Crohn's disease (CPMP/EWP/2284/99 Rev. 1)

Agreed by Gastroenterology Drafting Group	September 2014
Adopted by CHMP for release for consultation	25 September 2014
Start of public consultation	1 October 2014
End of consultation (deadline for comments)	31 December 2014

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8 The proposed guideline will replace the guideline on the development of new medicinal products for the
9 treatment of Crohn's disease (CPMP/EWP/2284/99 Rev. 1).

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

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

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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 (43-60%), followed by disease in the ileum only (19-35%), and in the colon only (20-25%). Upper gastro intestinal tract (17-33 %) is variable involved (as these patients differ from patients with more distal disease in terms of symptomatology and response to drugs, the current guideline is not applicable to patients with involvement of stomach and duodenum only). Symptoms are abdominal pain, diarrhoea, blood in stools, perianal disease and extraintestinal manifestations. The pathophysiological basis of the disorder is still incompletely understood, but inflammatory changes, selected immunological deficiencies, and genetic polymorphisms are involved.

2. Problem statement

The "Guideline on the development of medicinal products for the treatment of Crohn's disease (CHMP/EWP/2284/99) currently requests clinical indices as the primary measure of efficacy. However, there is growing evidence that mucosal healing as judged endoscopically, histologically or via imaging techniques reflects long term clinical outcome better than remission/response based on classical clinical indices such as CDAI.

The current guideline only includes more general comments for the conduct of clinical studies in children. In 2010, an expert meeting of European experts in paediatric gastroenterology and rheumatology published a statement, which in some areas is more demanding as regards the needs of and the mode of conduct of paediatric studies in Crohn's disease than the guideline document, leading to obvious discrepancies, with a subsequent need of reconciliation.

Furthermore, during the last decade there has been increasing discrepancy between the adult part of the current guideline and development plans presented for new drugs. In particular, the current guideline's request for separate studies aiming at demonstrating efficacy in the induction and the maintenance of remission settings has been questioned.

3. Discussion (on the problem statement)

Endpoints in clinical trials in adults and children:

Increasing evidence from studies in both adults and children indicates that morphological endpoints (i.e. mucosal healing) reflect long term outcome better than clinical indices such as CDAI/PCDAI. This growing awareness is also reflected in the previously mentioned Expert Statement, which recommends the use of endoscopy. The PCDAI as well as the CDAI have been challenged for flaws and validation is obviously still incomplete as already stated in the current Guideline. A thorough evaluation of the available data on validity and feasibility of mucosal healing (alone or in combination with clinical remission and/or biomarkers) as a primary measure of efficacy has therefore to be made.

Extrapolation of data from studies in adults to the paediatric situation:

Currently, the Guideline only generally states, "studies in children are encouraged". The main problem, namely the question whether and to what extent extrapolation from adults is possible, remains largely unexplored. Contrary to this, the above-mentioned Expert Statement clearly states that "extrapolation from adult studies is limited" and that in most cases separate studies in children are needed. It is therefore intended to evaluate whether more clear statements should be included into the guideline, as

to what extent extrapolation of adult data is possible, and whether criteria for extrapolation can be defined. Emerging scientific data on similarities and discrepancies between adult and paediatric disease have to be evaluated including differential drug effects as regards efficacy and safety.

Design of the studies in children:

Currently, the Crohn's disease guideline does not include a separate statement on the need or preference for placebo- or actively controlled studies in children. Contrary to this, the a.m. Expert Statement clearly prefers the conduct of actively controlled studies whenever feasible. Therefore, it has to be evaluated whether this question needs to be dealt with in a different way in children, as compared to adults. In the same context alternative study designs, such as withdrawal-, mono therapy-, comparator design and "add-on-studies" need to be evaluated for their suitability in paediatric drug development. Evaluation of previous dossiers demonstrated a need for re-assessment of PK/PD models due to unexplained discrepancies in outcome between children and adults. The number of patients included was insufficient to support any firm conclusions regarding doses and dosing intervals in children, although available data did suggest a need for higher doses and shorter dosing intervals. A separate paragraph on the need to explore PK and PK-PD relationship according to age and different pathophysiology might be necessary.

Design of studies (in both adults and children):

Traditionally, adult studies have been presented, and are requested by the current guideline, as separate induction and maintenance studies. This reflects the current recommendations from learned societies that the aim of treatment is inducing remission in the first place, and keeping the patient in remission in the second place. However, the reality of applications for new compounds during the last 10 years has brought about the presentation of data integrating the investigation of induction and remission in only one long-term study. Historically, the distinction between induction and maintenance of remission has also to be attributed to the mode of and onset of action of the traditional compounds used in the treatment of CD, namely corticosteroids and immunosuppressants (e.g. azathioprine). A thorough evaluation has to be undertaken whether the guideline should still include the request to clearly divide the two parts of CD treatment, or whether a more simple evaluation could also serve the needs. A reflection of the possible claims for new substances goes along with the reflection and potential changes of the trial designs.

4. Recommendation

The Gastroenterology Drafting group recommends the revision of the Guideline for conduct of studies for Crohn's Disease, Points to Consider on the evaluation of medicinal products for the treatment of Crohn's Disease.

Points to be addressed and evaluated concern the following fields:

1.) The examination and potential revision of the recommendations for the primary and secondary endpoints and for the principal design of the trials (including the comparator to be used).

2.) The need for more clear guidance as regards the possibility for extrapolation from adults, or the need to generate separate data in children. In the latter case, the scope of the studies needed, including design and comparator needs to be described.

3.) The need for inclusion of recommendations regarding exploration of PK/PD relationship in paediatric drug development, including the need for adaptation of the PK/PD model concerning dose finding.

4.) As regards both children and adults, the need for changes of the potential claims for new compounds (induction of remission/maintenance versus treatment indication) and consequences for trial design.

5. Proposed timetable

It is anticipated that a new draft CHMP Guideline may be available 12 months after adoption of the concept paper. The draft CHMP guideline will then be released for 6 months for external consultation and following receipt of comments it will be finalised in approximately 6 months. Finalisation will therefore be awaited for the second half of 2016.

6. Resource requirements for preparation

The preparation of the revision of the guideline will primarily involve the Gastroenterology Drafting Group.

7. Impact assessment (anticipated)

The revised guideline will provide updated guidance to both industry and Regulatory Authorities regarding the clinical development and assessment of medicinal products for the treatment of Crohn's Disease in the adult and paediatric population. This is expected to contribute to higher consistency in the development of new products in the field.

8. Interested parties

European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)

European Crohn and Colitis Organisation (ECCO)

United European Gastroenterology Federation (UEG)

9. References to literature, guidelines, etc.

EMA paediatric gastroenterology and rheumatology expert meeting London, 28-06 2010 (Ref. EMA/416878/2010)

Guideline on the development of new medicinal products for the treatment of Crohn's disease (Ref. CPMP/EWP/2284/99 Rev. 1)

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