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Rheumatology and Immunology Working Party (RIWP)

Concept paper on a paediatric update of the Guideline on clinical investigation of medicinal products for the management of Crohn's disease

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Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Introduction

Crohn's disease (CD) is a chronic relapsing, remitting inflammatory disease of the gastrointestinal tract. It occurs in all age groups, but with a higher incidence in the younger population. Although multiple medicinal treatment options are currently available for adults with CD, the medicinal treatment options for children are still limited. Paediatric drug development in CD faces numerous challenges, which are likely to delay the availability of authorized medicinal products for the paediatric population. To enhance the development and ultimately regulatory approval of medicinal products for paediatric CD patients, the sections of the current EMA Guideline on the development of new medicinal products for the treatment of Crohn's disease (CPMP/EWP/2284/99 Rev. 2)(1) related to the paediatric population will be reconsidered and updated where necessary.

1. Problem statement

Paediatric CD patients are likely to benefit from medicinal treatment options that are available for adult CD patients. There is substantial overlap in gene expression and disease characteristics between paediatric and adult inflammatory bowel disease populations (2, 3). Although the disease tends to be more extensive in paediatric compared to adult patients with a higher need for more advanced treatment options (e.g. biological treatment) (1, 4), the responses to pharmaceutical therapies may be comparable in both age groups. The similarity in pathophysiology between adult and paediatric CD can serve as a basis for extrapolation of efficacy and/or safety data of a medicinal treatment from adult to paediatric CD patients, taking into account the aspects addressed in the ICH E11A guidance such as potential differences in exposure-response by age and body weight (6).

Despite the similarities between adult and paediatric CD, the development and regulatory approval of new medicinal product for paediatric CD patients remains challenging after prior marketing authorisation in adult CD patients. There are difficulties to obtain paediatric data in this situation, which results in a delayed regulatory approval of the medicinal products for paediatric CD patients (4, 5). In order to facilitate timely development and authorization of medicinal products for paediatric CD patients, the regulatory requirements for this population should be reconsidered (4, 5).

Several factors have been identified that may complicate conducting clinical trials in the paediatric CD population after marketing authorisation of the medicinal product for adult CD patients. The potential allocation to placebo treatment can be a reason not to participate in a paediatric trial on CD once efficacy at an acceptable safety level of the new medicinal product has been demonstrated in adult CD patients, due to off-label paediatric use, the availability of suitable alternative medicinal products, and ethical reasons (4, 5). Therefore, the conditions in which a placebo arm would be acceptable in paediatric CD trials should be reconsidered (4, 5).

Another aspect to reconsider is the recommended efficacy endpoints in paediatric patients (4, 5). In the current EMA Guideline on the development of new medicinal products for the treatment of Crohn's disease (CPMP/EWP/2284/99 Rev. 2) (1), the requested co-primary endpoints are defined in terms of symptomatic and endoscopic remission, both for the induction and the maintenance phase of treatment. This need for repeated endoscopic procedures and the associated burden (including bowel preparation, anxiety, and absence from school or work) have been identified as an obstacle for recruitment of paediatric patients into CD trials. This results in delays in the development of medicinal products for the treatment of paediatric CD (5).

Non-invasive efficacy measures are currently available and have been increasingly accepted in the scientific community. Replacement of burdensome procedures by non-invasive measures in order to

reduce the frequency of ileocolonoscopies has the potential to enhance patient recruitment (4, 5). The value of the non-invasive efficacy measures should, however, be convincingly demonstrated.

Updated guidance on the use of registry data as part of the paediatric extrapolation plan, in line with the ICH E11A guidance, may be needed (1, 5, 6), as this may facilitate marketing authorisation of a new medicinal product in paediatric CD patients.

This concept paper highlights the points in the existing EMA guideline that may need to be revised to provide further guidance on when to and how clinical data in paediatric CD patients need to be generated, and how current challenges in conducting corresponding trials can be better addressed. The proposed update primarily concerns the sections of the CD guideline related to the paediatric population. If adjustments to the paediatric section also affect other sections of the guideline, respective sections will also be adjusted.

2. Discussion (on the problem statement)

The current regulatory requirements for development and approval of medicinal products for paediatric CD will be reconsidered in the light of the concerns identified and presented in the above section 1. of this document.

The following aspects would need to be addressed in the guideline update:

- Consideration to make it more explicit that extrapolation based on efficacy and safety established in adult CD, with paediatric pharmacokinetic and pharmacodynamic data, should be considered as a possibility to spare children from unnecessary trials;
- Consideration to make it more explicit in which situations extrapolation of efficacy data from adult CD patients is not considered possible, and a paediatric trial that is designed and powered to provide self-standing evidence on clinical efficacy would be needed;
- Reconsideration of the conditions in which a relevant control group (active or placebo arm) would be acceptable (or even necessary) in CD paediatric trials;
- Reconsideration of the need for ileocolonoscopy after induction and/or maintenance treatment to evaluate efficacy in paediatric clinical trials;
- Reconsideration of the value of non-invasive measurements of efficacy such as the Mucosal Inflammation Non-Invasive (MINI) index, TUMMY-CD index (patient-reported outcome measure), ultrasound, magnetic resonance enterography at baseline, at the end of induction and/or maintenance treatment;
- Consideration of the possibility that observational data could support extrapolation of evidence from adult to paediatric CD patients.

3. Recommendation

The Rheumatology and Immunology Working Party recommends revising the paediatric sections of the EMA Guideline on the development of new medicinal products for the treatment of Crohn's disease (CPMP/EWP/2284/99 Rev. 2) taking into account the specific issues identified above. To be more specific, the regulatory requirements with respect to data applicable to the paediatric setting and how the regulatory view on extrapolation from adult to paediatric patients is expressed (section 7.3.1 "Studies in paediatric patients" and its subsections) will be reconsidered. Based on these reconsiderations, it will be decided which adjustments or clarifications are needed to facilitate the

development of medicinal products for paediatric CD. Impact on other sections than section 7.3.1. will be assessed.

The current regulatory requirements for the development of medicinal products for adult CD patients are still considered to be generally appropriate.

4. Proposed timetable

Agreed by RIWP 7/2025, CHMP adoption for 2 months public consultation [to be determined]

Released for consultation on [to be determined].

5. Resource requirements for preparation

The resources needed relate to members of the drafting group who will reconsider the text in the current paediatric section of the EMA guideline on Crohn's disease (1) and who will propose adjustments to this section where necessary.

6. Impact assessment (anticipated)

The most important impact is expected to be on:

- Promotion of adequate development and approval of medicinal products for paediatric CD patients.
- The regulatory requirements for the clinical development of medicinal products for paediatric CD.
- The willingness of paediatric patients and their caregivers to participate in clinical studies for the development of medicinal products for paediatric CD.
- The content of CHMP scientific advice and paediatric investigation plans.

7. Interested parties

- Patient organisations;
- Healthcare professionals;
- Academic networks and learned societies within the European Union, e.g. the European Crohn's and Colitis Organisation (ECCO), European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), and national professional societies for inflammatory bowel disease;
- Pharmaceutical industry;
- EU competent authorities;
- Consultation with other working parties or committees (e.g. scientific advice working party (SAWP), methodology working party (MWP)) will be initiated, as appropriate;
- International regulatory agencies.

8. References to literature, guidelines, etc.

1. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Guideline on the development of new medicinal products for the treatment of Crohn's Disease, 2018.

2. Li K, Strauss R, Ouahed J, et al. Molecular Comparison of Adult and Pediatric Ulcerative Colitis Indicates Broad Similarity of Molecular Pathways in Disease Tissue. Journal of Pediatric Gastroenterology and Nutrition 2018;67(1):45-52.

3. Markowitz J. Early inflammatory bowel disease: different treatment response to specific or all medications? Dig Dis. 2009;27(3):358-65.

4. Turner D et al. Designing clinical trials in paediatric inflammatory bowel diseases: a PIBDnet commentary. Gut 2020; 69: 32-41.

5. Croft NM et al. A multi-stakeholder perspective to improve development of drugs for children and adolescents. Journal of Crohn's and Colitis. 2023; 17: 249-258.

6. ICH guideline E11A on pediatric extrapolation Step 5 (EMA/CHMP/ICH/205218/2022).