Administrative Notice
March 24, 2025

To (Note)

Pharmaceuticals and Medical Devices Agency
Office of New Drug I

"Points to Consider in Developing Drugs for Pediatric Inflammatory Bowel Disease (Early Consideration)"

Thank you for your cooperation in reviewing operations conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

PMDA has been supporting development through "Pediatric/Orphan Drug Regulatory Affairs Consultation Center Business" to ensure early access of pediatrics to useful drugs.

To date, multiple therapeutic agents for inflammatory bowel disease (IBD) have been approved in Japan; however, the majority of such agents are based on the results of clinical studies in adult patients with IBD. The pediatric dosage and administration have not been investigated. Hence, there are not as many options of drugs approved for pediatric IBD patients as those for adult IBD patients at present.

Based on the above situation, PMDA has identified the points to consider in planning clinical studies to develop drugs for pediatric IBD as shown in the Attachment.

It should be noted that Early Consideration is merely an idea at the time concerned that is presented as reference information to promote practical application of innovations including novel technologies and development of innovative drugs. However, scientific knowledge or information has not necessarily been accumulated and is subject to change depending on new knowledge obtained in the future or scientific advancements.

(Note)

The Federation of Pharmaceutical Manufacturers' Associations of JAPAN
Japan Pharmaceutical Manufacturers Association
Japan-Based Executive Committee of Pharmaceutical Research and Manufacturers of America
European Federation of Pharmaceutical Industries and Associations

Points to Consider in Developing Drugs for Pediatric Inflammatory Bowel Disease
(Early Consideration)

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1. Introduction

In Japan, the promotion of pediatric drug development is one of the issues to be prioritized at present. Generally, however, there are more issues compared to drug development for adults, such as smaller patient populations. The development of drugs for pediatric inflammatory bowel disease (IBD) (ulcerative colitis [UC] and Crohn's disease [CD]) has further issues. Because endoscopy required for diagnosis or activity assessment is a greater burden for children than adults, subjective symptoms cannot be assessed by the same assessment index as that for adults.

Recently, drugs for adult IBD have been actively developed for both UC and CD. Particularly for moderate to severe IBD, various drugs with different mechanisms of action have been approved (e.g., biological drugs [anti-tumor necrosis factor alfa antibody, anti-integrin antibody, anti-interleukin {IL}-12/23p40 antibody, anti-IL-23p19 antibody], janus kinase [JAK] inhibitor, sphingosine 1-phosphate [S1P] receptor modulator etc.), increasing the number of treatment options in clinical practice every year. However, as for the most approved therapeutic drugs for IBD, the population studied in the clinical studies that served as the rationale for regulatory approval was patients aged 18 years or older, and pediatric dosage and administration have not been investigated. Therefore, their package inserts call attention in the section "PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS" that no clinical study in pediatrics has been conducted. This means that there are not as many regulatory-approved drugs for pediatric IBD as those for adult IBD at present.

This "Points to Consider" document is intended to present a basic idea for the development of pediatric IBD drugs so that such development is promoted. For development of drugs for pediatric patients, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) issued "Clinical Investigation of Medicinal Products in the Pediatric Population" (ICH E11) and its addendum[1), 2), 3)]. This "Points to Consider" shall follow them. With regard to individual clinical studies of drugs in pediatric IBD patients, it is considered that the appropriate design is different depending on the information obtained, such as the results of clinical studies in adult IBD patients, as of the time when a pediatric clinical study is planned. Therefore, it is recommended to plan each individual clinical study using consultations with the Pharmaceuticals and Medical Devices Agency (PMDA). It should be noted that the concepts presented in this "Points to Consider" is subject to change depending on new knowledge etc. obtained in the future.

2. Points to Consider in Developing Drugs for Pediatric Inflammatory Bowel Disease

2.1. General matters

In the development of drugs for pediatric UC or CD, it is necessary in principle to conduct clinical studies with the purpose of investigating the efficacy, safety, and pharmacokinetics of the drug under development in pediatric patients with UC or CD. However, due to the small population, it is difficult to design clinical studies in pediatric UC and CD patients to obtain sufficient evidence in some cases.

In IBD, the pathophysiology and diagnostic criteria for UC and CD are similar between pediatrics and adults. The treatment goal (improvement or remission of symptoms in a short term, and maintenance of clinical and endoscopic remission in the long term) is also common between pediatrics and adults (Diagnostic Criteria/Clinical Practice Guidelines for Ulcerative Colitis/Crohn's Disease 2023)[4]. Based on the above background, in some cases of drugs for which development for adult UC and/or CD patients is already underway, the results of clinical studies in adult patients may be used in part to explain the efficacy and safety of the drug concerned in pediatric patients. In such cases, it is necessary for the developer to consider potential factors likely to cause different responses to the drug between pediatrics and adults, and then to fully explain the appropriateness of using the results of clinical studies in adult patients as a part of information to explain the efficacy and safety in pediatric patients. Furthermore, in clinical studies in pediatric patients, the severity of patients to be studied, endpoints, assessment timing etc. should be the same as those in clinical studies in adults as much as possible so that it is easier to compare pediatric results and adult results. Additionally, after the results of clinical studies in pediatric patients are obtained, the following should be explained.

- There is no evident difference in the efficacy and safety between the results of clinical studies in pediatrics and the results of clinical studies in adults.
- There is no evident difference in the pharmacokinetics of the drug under development between pediatric patients and adult patients.

2.2. Patients to be studied in clinical studies

- Age

  Based on the age of pediatric patients who may receive the drug under development in actual clinical settings, the study population should include patients of various ages as much as possible. As specified in “Considerations for the Clinical Evaluation of Drugs in Pediatric Patients (10 or 12 Years of Age and Older) Who Can be Evaluated Together with Adults” (Administrative Notice dated June 30, 2020 by Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)[5], it is preferred to include pediatric patients in the adult clinical study to evaluate the efficacy and safety in pediatrics together with adults patients in the following cases: Pediatric patients aged 10 or 12

years of age and older are considered to be exposed to the drug concerned at the same level as adults, the dosage and administration are expected to be similar to those of adults, and the same drug is available.

- Diagnosis

  It is appropriate to include patients with a definitive diagnosis of UC or CD for whom other diseases than IBD are ruled out based on endoscopic and biopsy-based histological findings.

- Severity

  Based on clinical positioning and the expected patients in actual clinical practice, the severity of target patients should be determined based on appropriately selected indices such as Mayo Score (MS) and modified Mayo Score (mMS) for UC and indices appropriately selected from indices such as Crohn's Disease Activity Index (CDAI), Pediatric Crohn's Disease Activity Index (PCDAI), and Simple Endoscopic Score for Crohn's Disease (SES-CD)[6] (Table 1) for CD. If the results of clinical studies in adult patients are used in part to explain the efficacy and safety of the drug concerned in pediatric patients, the severity of pediatric patients should be the same as the severity defined in the clinical study in adult patients.

Table 1 Outline of Major Index for Pediatric IBD Activity Evaluation

	Index	Outline of Index
Ulcerative colitis (UC)	**Mayo Score (MS)**	**Composite score consisting of subscores of "stool frequency," "rectal bleeding," "endoscopy," and "physician's global assessment"**
	modified Mayo Score (mMS)	**Composite score consisting of 4 MS subscores except "physician's global assessment"**
Crohn's disease (CD)	**Crohn's Disease Activity Index (CDAI)**	**Composite score consisting of subscores of "stool frequency," "abdominal pain," "global health status," "extraintestinal complications," "use of antidiarrheal medications," "abdominal mass," "hematocrit" and "weight"**
	Pediatric Crohn's Disease Activity Index (PCDAI)	**Composite score consisting of subscores of "abdominal pain," "patient function, global health status," "stool frequency and form," "hematocrit," "erythrocyte sedimentation," "albumin," "weight," "height," "abdominal pain, abdominal mass," "perirectal lesion," and "extraintestinal complications"**
	Simple Endoscopic Score for Crohn's Disease (SES-CD)	**Composite score consisting of subscores of "size of ulcer," "area of ulcer," "area of lesion," and "presence/absence of stenosis"**

- Treatment history

  The inclusion/exclusion criteria related to the treatment history should be established based on the clinical positioning and target patients expected in actual clinical practice as well as the treatment history of pediatric patients in the actual clinical setting. If patients previously treated

with biological products are included in clinical studies, it is desirable to determine the proportion of patients to be enrolled by presence/absence of treatment history in advance. If the results of clinical studies in adult patients are used in part to explain the efficacy and safety of the drug concerned in pediatric patients, it is preferred that the proportion of patients previously treated/untreated with biological products is the same as that in the clinical study in adult patients if possible in light of the difference in the usage status of biological products in actual clinical practice between pediatric patients and adult patients as of the time of planning the clinical study.

2.3. Clinical Study Design

In principle, the conduct of randomized controlled studies should be considered. Even in cases where it is difficult to conduct a domestic randomized controlled study in Japan due to the number of participants, it may be possible to conduct a global randomized controlled study. Therefore, the conduct of a global randomized controlled study and participation in such a study should be considered. If it is considered extremely infeasible to conduct a randomized controlled study based on the results of an appropriate feasibility survey, the conduct of a single-arm study may be an option. For instance, if the experience of use of the drugs under development has been accumulated in pediatric patients and the enrollment in a placebo-controlled randomized study cannot be expected, it is possible to select a single-arm study.

The study period should be at least 1 year for drugs expected to be used for long-term to maintain remission so that the long-term efficacy and safety can be assessed.

- Dose Selection

  If the results of clinical studies in adult patients are already available, the data on the dose/exposure-response relationship in the clinical studies in adult patients should be referred to when selecting the dose in a clinical study in pediatric patients. However, when it is uncertain whether or not the dose/exposure-response relationship similar to that in adult patients is established in pediatric patients, additional information is required. For instance, if there are pediatric pharmacokinetic data of the drug concerned in other diseases than IBD, such data may be used to determine the dose for pediatric UC or CD patients.

- Sample size

  If a global study is planned, participation from Japan should be considered. When taking part in a global study, it is recommended to set the Japanese sample size in consideration of the balance in the entire study (balance with the planned sample size in other participating countries) and the feasibility, taking into account the evaluation of consistency of results between the entire population and the Japanese population.

If a clinical study in pediatric patients is conducted as a domestic study in Japan, the target sample size should be able to ensure a sufficient power, although the feasibility should be considered. If a clinical study in pediatric patients is conducted as a domestic study in Japan and the results of clinical studies in adult patients or the results of overseas studies are used as a part of efficacy and safety data, the sample size should be defined so as to obtain results that can be comparable with the results of clinical studies in adult patients or overseas clinical studies.

In both global studies and domestic studies in Japan, a sample size with appropriate age groups should be set as much as possible to evaluate the efficacy and safety in each of the age groups.

2.4. Efficacy evaluation

- Efficacy Endpoints

In the treatment of IBD, treatment intended for remission induction is provided during the active phase for both UC and CD. After remission induction, treatment to maintain remission is continued long-term[4)]. As for drugs expected to be used throughout the induction and maintenance phases, it is necessary to appropriately evaluate the efficacy during both induction and maintenance phases. If the primary endpoint is intended for only one of the induction phases and the maintenance phase, another one should be defined as a secondary endpoint and evaluated. If the primary endpoint is intended for only one of the induction phases and the maintenance phase, the maintenance phase is prioritized as the primary endpoint. It is recommended to set the primary endpoint in consideration of the impact on the indication at the time of marketing approval.

In clinical studies in UC patients, it is recommended to evaluate "clinical remission" based on indices such as MS and mMS as the primary endpoint, and "clinical improvement," "steroid-free remission," "endoscopic improvement," "endoscopic remission," and "maintenance of clinical remission" as secondary endpoints. With regard to endoscopy, it is desirable to perform a total colonoscopy wherever possible, although the burden of the examination for pediatric patients needs to be considered.

In clinical studies in CD patients, although feasibility must be taken into account, it is recommended to define co-primary endpoints consisting of [1] "clinical remission" based on indices such as CDAI and PCDAI and [2] "endoscopic remission" or "endoscopic improvement" based on indices such as SES-CD with the purpose of demonstrating the efficacy for both endpoints. As the secondary endpoint, it is recommended to evaluate "clinical improvement," "steroid-free remission," "endoscopic improvement" (if not defined as the primary endpoint), "endoscopic remission" (if not defined as the primary endpoint), and "maintenance of clinical remission".

If the results of clinical studies in adult patients are used as a part of information for efficacy

evaluation in pediatric patients, the primary and secondary endpoints, including the evaluation time points (induction phase, maintenance phase), in clinical studies in pediatric patients should be similar to those in clinical studies in adult patients so that it is easier to compare the results of clinical studies between pediatric patients and adult patients (See Section 2.1).

- Statistical Analysis Plan

  As in general clinical studies, the plan for statistical analysis in clinical studies in pediatric patients should be specified beforehand, and its details should be included in the protocol and/or statistical analysis plan, according to the positioning of analyses[7]. Particularly, in the case where a single-arm study is conducted based on the feasibility of clinical studies in pediatric patients (see Section 2.3), it is preferred to specify the details of the statistical analysis plan for the primary and key secondary analyses before the start of the study (before the enrollment of first participant).

  The primary analysis of the primary endpoint should be generally based on statistical hypothesis testing, etc. Even if sufficient power cannot be expected from the viewpoint of feasibility, such as the number of patients, at least the criteria for study success based on statistical considerations should be defined in advance. Particularly, concerning the primary analysis in the case where a single-arm study is conducted, the primary endpoint should demonstrate that the efficacy of the study drug exceeds the prespecified threshold. In this case, it is recommended to use methods such as statistical hypothesis testing. If sufficient power cannot be ensured, at least the criteria for study success by comparison with a threshold based on statistical consideration, such as estimation-based methods etc., should be defined in advance. The threshold may be set with reference to the results of [1] the placebo group in randomized clinical studies of the drug under development in adult patients and [2] meta-analysis of the placebo group in randomized controlled studies of other drugs in pediatric patients or adult patients with the same severity and treatment history as those in the planned clinical study in pediatric patients.

  It is important to clarify the estimand, including the population (see Section 2.2) and the primary endpoint, in advance. The primary estimand corresponding to the primary objective of the clinical study should be clearly defined in the protocol, and appropriate sensitivity analyses should also be predetermined[8] after the definition and handling of interim events, such as the discontinuation of the investigational drug, is considered. The handling of missing data should be specified in advance, too.

  In the evaluation of the results obtained in clinical studies in pediatric patients, a comprehensive evaluation including not only the primary analysis on the primary endpoints but also the secondary endpoints are important, just as in general clinical studies. Particularly in studies with insufficient power due to the feasibility, the importance of comprehensive evaluation increases. In addition, if the results of clinical studies in adult patients are used in part to explain

the efficacy of the drug concerned in pediatric patients, it is necessary to confirm that the results of the clinical study in pediatric patients and the results of the clinical study in adult patients are not evidently different in terms of the efficacy (see Section 2.1).

2.5. Safety evaluation

- Consideration for growth failure–

  Growth failure should be taken into consideration in the treatment of pediatric IBD, and the use of corticosteroids that cause growth failure should be kept as short as possible[4]. In clinical studies in pediatric patients, it is preferred to confirm the indices of growth such as secondary sexual characteristics and bone age, if possible, in addition to height and body weight in terms of confirming the effects on growth.

- Long-term safety evaluation

  For drugs expected to be used long-term to maintain remission, the long-term safety should be evaluated based on the results of clinical studies with a treatment period of at least 1 year.

[Reference]

1) “Clinical Investigation of Medicinal Products in the Pediatric Population” (PMSB/ELD Notification No. 1334 dated December 15, 2000)
2) “Questions and Answers on Clinical Investigation of Medicinal Products for the Pediatric Population” (Administrative Notice by Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health, Labour and Welfare dated June 22, 2001)
3) “Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population” (PSEHB/ELD Notification No. 1227-5 dated December 27, 2017)
4) “Diagnostic Criteria/Clinical Practice Guidelines for Ulcerative Colitis/Crohn’s Disease 2024 Revised Edition (March 31, 2024)”: Health and Labour Sciences Research Grant for Research Project on Rare and Intractable Diseases “Investigation on Refractory Inflammatory Bowel Disease” (Hisamatsu Group) Fiscal Year 2023 2005 General Partial Research Report
5) “Considerations for the Clinical Evaluation of Drugs in Pediatric Patients (10 or 12 Years of Age and Older) Who Can be Evaluated Together with Adults” (Administrative Notice dated June 30, 2020 by Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
6) “Indices for Inflammatory Bowel Disease Activity Evaluation 2nd Edition (March 2020): Health and Labour Sciences Research Grant for Research Project on Rare and Intractable Diseases “Investigation on Refractory Inflammatory Bowel Disease” (Suzuki Group)
7) “Statistical Principles for Clinical Trials” (PMSB/ELD Notification No. 1047 dated November

30, 1998)

8) “Addendum for Statistical Principles for Clinical Trials” (PSB/PED Notification No. 0620-1 dated June 20, 2024)