Provisional Translation (as of November 2025) *

Points to Consider for Clinical Development of Drugs Intended for Treatment of Psoriatic Arthritis (Early Consideration)

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1. Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease characterized by joint symptoms and psoriasis, an inflammatory keratosis. The predominant joint manifestation is enthesitis, an inflammation occurring at the sites where tendons, ligaments, and other soft tissues attach to bone. These joint symptoms are observed not only in peripheral joints but also in axial joints such as the spine. Other characteristic features of PsA include nail psoriasis and dactylitis, which results from friction between the phalanges and surrounding tendons or ligaments. Currently, PsA is regarded as a subtype of spondyloarthritis, classified as a peripheral spondyloarthritis phenotype in which peripheral arthritis predominates over axial arthritis[1),2)].

According to the Japanese PsA clinical practice guidelines ("PsA 診療ガイドライン"[1)] and "脊椎関節炎診療の手引き"[2)]), published in 2019 and 2020 respectively, the treatment goals for PsA include improvement in patients' quality of life through alleviation or resolution of joint symptoms, as well as prevention of irreversible joint destruction, and these documents emphasize the importance of managing joint symptoms in PsA treatment. In the implementation of treat-to-target (T2T) approaches, which include setting the specific treatment goals and timelines, remission, defined as the absence of disease activity in PsA, should ideally be the target. However, given the difficulty in achieving remission in many patients, treatment decisions are often guided by the more attainable goals of minimal or low disease activity.

On the other hand, in recent years, the development of PsA therapeutics has become increasingly globalized in Japan, similar to other disease areas. Consequently, applications for PsA therapeutics have been filed based on data from multi-regional clinical trials (MRCTs) involving PsA patients.

This document outlines key considerations that the Pharmaceuticals and Medical Devices Agency (PMDA) deems important for the clinical development of PsA therapeutics, based on domestic clinical practice guidelines for PsA, recent changes in Japan's drug development landscape, and accumulated scientific knowledge to date. It should be noted that the considerations presented in this document are based on the current body of knowledge and may be subject to change as new evidence emerges. Furthermore, sponsors are encouraged to discuss clinical development plans—including clinical trial protocols and data packages—for individual investigational drug products with the PMDA.

* This English version of the Japanese Early consideration is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail

2. Considerations for Development Strategy

Given that the prevalence of PsA among patients with psoriasis in Japan has been reported to be approximately 8 to 13%[3], it is anticipated that conducting a confirmatory trial with a sufficient sample size to evaluate efficacy and safety solely within Japan would be challenging. For PsA, since there are no significant domestic or international differences in the pathology, diagnosis, and treatment paradigms[1),4),5)], it is recommended that MRCTs be actively considered from the early stage, following an evaluation of potential ethnic differences in pharmacokinetics and other factors for each investigational drug. It is recommended that sponsors consult with the PMDA regarding their development strategy when Japan's participation in the MRCTs is deemed inappropriate or concerns arise, such as the observation of ethnic differences in the pharmacokinetics of the investigational medical product.

3. Considerations for Confirmatory trials

3.1. Study Design

Confirmatory trials for PsA should be designed as randomized, double-blind, controlled trials, with appropriate control group(s), selected based on the anticipated clinical positioning of the investigational drug within the treatment paradigm for PsA. While an active comparator using an existing medicinal product with a similar clinical positioning may be considered, a placebo control is generally expected to be employed.

3.2. Study Population

In confirmatory trials, inclusion and exclusion criteria must be established to ensure the selection of patients appropriate for evaluating the efficacy and safety of the investigational drug in the target patient population anticipated in clinical practice.

Considering the treatment paradigm for PsA, the target patient population in clinical practice may include, for example, patients who have shown inadequate response to conventional treatments (Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), conventional synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs)), but have not previously received biologics (Bio-Naïve patients), as well as those who have shown insufficient response to biologic treatment in addition to conventional treatments (Bio-IR patients). If an investigational drug is intended for use in both of these populations, it is appropriate to evaluate its efficacy and safety in each population. In such a case, conducting separate confirmatory trials for each population is one option; alternatively, if prior exploratory trials have demonstrated no significant differences in the efficacy and safety between both populations, a single confirmatory trial covering both populations may be considered. When adopting the latter strategy, it is preferable to perform stratified randomization using "Bio-Naïve patients/Bio-IR patients" as stratification factors to enhance the comparability between subgroups.

3.3. Efficacy Endpoints

In confirmatory trials, it is considered ideal to evaluate whether the treatment goals of achieving minimal disease or low disease activity—central to the treat-to-target strategy as mentioned in Section 1—can be attained. However, due to the absence of a comprehensive index capable of evaluating the diverse clinical

symptoms of PsA, most current clinical trials adopt the American College of Rheumatology (ACR) core set—focused on joint symptoms critical to PsA management—as the primary endpoint (ACR response rate)**. Secondary endpoints include assessments of enthesitis, dactylitis, nail psoriasis, and psoriatic skin lesions, with overall efficacy determined based on these combined outcomes.

In recent years, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has proposed the Minimal Disease Activity (MDA) criteria*** as an index for assessing minimal disease activity. These MDA criteria represent a composite measure that enables evaluations not only of joint symptoms but also of enthesitis and psoriatic skin lesions. The European Medicines Agency (EMA) has issued documentation supporting the use of MDA criteria as a primary endpoint[7]. Given its potential to comprehensively assess the diverse clinical manifestations of PsA, the MDA criteria have already been employed as secondary endpoints in the development of several therapeutic drugs. However, in Japan, since consensus among stakeholders from academia, industry, and regulatory agency has not yet been established regarding the validity of the MDA criteria, including the clinical relevance of its outcomes and correlations with other efficacy endpoints, it does not seem to be at a stage where the use of MDA as a primary endpoint in confirmatory trials can be actively recommended.

Therefore, at present, it is considered appropriate to adopt the ACR response rate as the primary endpoint in the confirmatory trial and to include MDA as secondary endpoints response criteria along with other endpoints capable of evaluating the diverse clinical manifestations of PsA. These results should be comprehensively evaluated to determine the efficacy of the investigational drug for PsA.

Recommendations regarding efficacy endpoints and timing of assessments are provided below.

＜Outcome Measures＞

Regarding the ACR response rate set as the primary endpoint, while higher thresholds (e.g., ACR20, 50, 70 response rate**) are desirable in light of the approval status of existing PsA treatments. It is appropriate to determine the specific threshold based on the benefit-risk balance of the investigational drug, its target population in clinical practice, and its clinical positioning.

For secondary endpoints, it is important to include outcome measures capable of capturing the diverse clinical symptoms of PsA. Specifically, in addition to the MDA criteria, other outcome measures exemplified in the table below should be considered.

Furthermore, in cases where the MDA criteria are to be adopted as a primary endpoint, it is recommended that consultation with the PMDA be conducted prior to study initiation, after their appropriateness has been carefully examined.

** Patients are classified as achieving ACRxx when there is at least xx% improvement from baseline in both the tender joint count and swollen joint count, and at least xx% improvement in 3 of the following 5 measures: patient pain assessment, patient global disease activity, physician global assessment, patient physical function, and an acute-phase reactant (erythrocyte sedimentation rate or CRP [C-reactive protein]).

*** Patients are classified as achieving MDA when meeting 5 of the 7 following criteria:
(1) tender joint count≦1, (2) swollen joint count≦1, (3) PASI (Psoriasis Activity and Severity Index) ≦1 or BSA (body surface area)≦3, (4) patient pain VAS (Visual Analog Scale)≦15, (5) patient global disease activity VAS≦20, (6) HAQ (Health Assessment Questionnaire) ≦0.5, (7) tender entheseal points≦1

Table　Example of secondary endpoints for the various clinical symptoms of PsA

Clinical signs	Outcome measures
Structural joint damage	modified Total Sharp Score (mTSS)
Enthesitis	Leeds Enthesitis Index (LEI)
Dactylitis	Leeds Dactylitis Index (LDI)
Axial arthritis	Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
Nail psoriasis	modified Nail Psoriasis Severity Index (mNAPSI)
Psoriatic skin lesions	Psoriasis Area and Severity Index (PASI)

＜Timing of Endpoints＞

Given that Japanese clinical practice guidelines recommend assessing treatment efficacy approximately 3 to 6 months after treatment initiation[1)], it is considered appropriate to set the assessment timing of the primary endpoint within 12 to 24 weeks of administration.

Furthermore, since PsA requires long-term treatment, it is important to evaluate additional time points such as at 52 weeks, in order to evaluate the long-term efficacy of the investigational drug beyond the primary endpoint assessment.

4. Considerations for Pediatric Drug Development

It is desirable that the drug development program targeting pediatric PsA patients be planned during the development of a drug for adult PsA patients. When planning the pediatric drug development program and the timing of consultations with the PMDA, please refer to the relevant notifications and related materials[8)].

In the development of drugs for pediatric PsA, depending on the information available at the time of development, clinical trials aimed at evaluating efficacy and safety in pediatric patients could be considered; additionally, extrapolation approaches and the use of modeling and simulation could also be appropriate.

While adult patients often present with cutaneous symptoms prior to joint symptoms, many pediatric patients exhibit joint symptoms as the initial symptoms. Despite these differences in disease onset, it is generally considered that the pathogenesis and clinical manifestations of pediatric PsA patients of school age and older (approximately 6 years and above) do not significantly differ from those of adult patients[1)]. Furthermore, although the number of approved drugs for pediatric PsA remains limited, there are no significant differences in the treatment approach between pediatric and adult patients[1)]. On the other hand, in the development of treatments for pediatric PsA, it is also anticipated that clinical development for pediatric psoriasis vulgaris (PsO) may be conducted in parallel with or prior to pediatric PsA, and that relevant data may already be available. Therefore, if the validity can be appropriately justified based on the existing clinical data for the investigational drug, it may be possible to build the clinical data package for pediatric PsA using extrapolation approaches that incorporate data from adult PsA and pediatric PsO populations.

When planning clinical trial(s) targeting pediatric PsA patients, it is recommended that Japan participate in the trial(s) and enroll as many Japanese patients as possible, provided that no significant ethnic differences are anticipated. However, given the limited number of pediatric PsA patients in Japan[9)], it is anticipated that the enrollment of Japanese pediatric PsA patients could be extremely low or even absent. Given the challenges in conducting additional clinical trials targeting Japanese pediatric PsA patients, it is necessary to carefully evaluate whether the efficacy and safety of the investigational drug for Japanese pediatric PsA

patients can be assessed based primarily on the clinical trial results derived from non-Japanese pediatric PsA patients. This assessment should also take into account the presence or absence of efficacy and safety differences between Japanese and non-Japanese adult PsA patients.

It is recommended that sponsors contact the PMDA for consultation on their development programs of pediatric PsA patients in advance.

5. References

1) 日本皮膚科学会乾癬性関節炎診療ガイドライン作成委員会, 厚生労働科学研究費補助金 難治性疾患等政策研究事業 乾癬性関節炎研究班. 日本皮膚科学会ガイドライン 乾癬性関節炎診療ガイドライン 2019. 日皮会誌 2019; 129: 2675-733
2) 日本脊椎関節炎学会, 厚生労働科学研究費補助金（難治性疾患政策研究事業）「強直性脊椎炎に代表される脊椎関節炎の疫学調査・診断基準作成と診療ガイドライン策定を目指した大規模多施設研究」班 編. 脊椎関節炎診療の手引き 2020. 株式会社 診断と治療社. 2020: 1-150
3) Umezawa Y. Psoriatic arthritis. J Dermatol. 2021; 48: 741-9
4) Gossec L, Kerschbaumer A, Ferreira RJO, Aletaha D, Baraliakos X, Bertheussen H, *et al*. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2023 update. Ann Rheum Dis. 2024; 83: 706-19
5) Coates LC, Soriano ER, Corp N, Bertheussen H, Duffin KC, Campanholo CB, *et al*. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. Nat Rev Rheumatol. 2022; 18: 465-79
6) Gossec L, McGonagle D, Korotaeva T, Lubrano E, de Miguel E, Østergaard M, *et al*. Minimal Disease Activity as a Treatment Target in Psoriatic Arthritis: A Review of the Literature. J Rheumatol. 2018; 45: 6-13
7) "Letter of support for Minimal Disease Activity Score (MDA) as primary outcome instrument for clinical studies in psoriatic arthritis (PsA)". (22 February 2022, EMADOC-1700519818-782278)
8) "Partial revision of "Planning of the Pediatric Drug Development Program during Development of Drugs for Adults"" PSB/PED Notification No. 0329-1 issued March 29, 2024, "Q & A for "Planning of the Pediatric Drug Development Program during Development of Drugs for Adults"" Administrative Notice issued March 29, 2024 by PSB/PED, "Clinical Investigation of Medicinal Products in the Pediatric Population" PMSB/ELD Notification No. 1334 issued December 15, 2000, "Q & A for "Clinical Investigation of Medicinal Products in the Pediatric Population"" Administrative Notice issued June 22, 2001 by PMSB/ELD, "Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population" PSEHB/PED Notification No. 1227-5 issued December 27, 2017
9) 一般社団法人日本リウマチ学会 編. 若年性特発性関節炎診療ガイドライン 2024-25 年版. 株式会社 メディカルレビュー社. 2025: 1-264