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Committee for medicinal products for human use (CHMP)

Concept paper on the need for revision of the guideline on clinical investigation of medicinal products for the treatment of psoriatic arthritis

Agreed by Rheumatology/Immunology Working Party	April 2024
Adopted by CHMP for release for consultation	17 June 2024
Start of public consultation	1 July 2024
End of consultation (deadline for comments)	30 September 2024

The proposed guideline will replace the Guideline on clinical investigation of medicinal products for the treatment of psoriatic arthritis (CHMP/EWP/438/04).

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	Psoriatic arthritis, treat-to target, extra musculoskeletal disease manifestations, guidance

1. Introduction

Psoriatic Arthritis (PsA) is a multifactorial, chronic inflammatory arthropathy of the peripheral and axial joints affecting synovium, tendons, entheses, skin and bone. Pain, inflammation and fatigue are a significant burden for patients. To prevent joint damage from persisting inflammation early treatment is indicated. In patients with Plaque Psoriasis (PsO) the prevalence of PsA is approximately 20%.[1,2]

The current Guideline on clinical investigation of medicinal products for the treatment of psoriatic arthritis[3] came into effect in 2007. Since then, several medicinal products have been approved in the EU for the treatment of PsA and consecutively there are also substantial updates in general treatment approaches and treatment goals for this condition[4]. Despite the number of existing treatment options for PsA, an unmet need still exists for patients experiencing poor efficacy and tolerability of current therapies.

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2. Problem statement

The regulatory guidance on the treatment of PsA has not been updated since 2007 and does not take into account the regulatory experience with applications for scientific advice and for marketing authorisation since then, or the current approaches of the pharmacological management of PsA[4] nor recent developments within the field of 'early' disease detection in the population at risk.

In particular, the European League Against Rheumatism (EULAR) recommendations for the treatment of PsA have been published and most recently updated[4]. EULAR points to consider for the definition of clinical and imaging features suspicious for progression from psoriasis to PsA[5] also need to be considered.

Therefore, several important additions and changes are needed to explicit the current state of scientific knowledge in the guideline.

The purpose of this concept paper is to highlight the identified points for revision of the existing Guideline on Clinical Investigation of Medicinal products for the treatment of psoriatic arthritis[3]. The guideline update concerns the adult form of PsA. The paediatric form is addressed by the Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis[6], that is not within the scope of the current guideline update.

3. Discussion (on the problem statement)

The following critical aspects have been identified and would need to be addressed in the revised guideline:

- Since the current EMA PsA guideline[3] came into effect, the PsA (and PsO) treatment armamentarium has expanded. Currently, many different medicinal products are approved for PsA in the EU. These include both conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and various biologics targeting tumour necrosis factor (TNF), Interleukin (IL)-17, IL-12/23, IL-23, and modulation of T lymphocyte-dependent antibody responses. An additional drug class comprises targeted synthetic DMARDs (tsDMARDs), that inhibit phosphodiesterase-4 (PDE4); and the Janus kinase (JAKs) i.e. JAK-inhibitors interfering with the JAK-STAT signalling pathway.

  Importantly, the regulatory experience from recent approvals in the PsA field may have generated essential insights that should be reflected in an update of the EMA PsA guideline including what can be considered reasonable standard of care, concomitant study treatment or rescue therapy, as well as potential active comparators in PsA-studies.

- The current EMA PsA guideline[3] states that there are no generally accepted validated case definitions of PsA and at present, the diagnosis is based on clinical judgement.

  The additional experience that has been gained since the guideline was issued may allow an update of this section of the guideline. The Classification criteria for Psoriatic Arthritis[7] is currently widely used, including in recent clinical trials in marketing authorisation applications for PsA.

- The EULAR developed recommendations for the pharmacological management of PsA in 2011[8] and updated them in 2015[9], 2019[10] and 2023[4]. The EULAR recommendation includes some important points that are either not reflected or not sufficiently addressed in the current EMA PsA guideline.

- First, the most recent EULAR publication[4] includes the following recommendation 'Treatment should be aimed at reaching the target of remission or, alternatively, low disease activity, by regular disease activity assessment and appropriate adjustment of therapy' i.e. a treat-to-target (T2T) approach. Also 'The taskforce members emphasised that disease activity should be regularly assessed across individual involved manifestations (eg, joints, skin, enthesitis, dactylitis, axial disease), and that treatment adjustments will depend on the predominant manifestation of the disease at a given moment.'

  To be noted, the EMA recently published a Letter of support for Minimal Disease Activity Score as primary outcome instrument for clinical studies in PsA[11] .

  Overall, a rather substantial revision of the guideline section on *'Methods to assess efficacy'* is expected, reflecting also validation and use of new endpoints in authorisation studies as compared to 2007 when the current guideline came into effect. It is foreseen that the recommendation for the primary endpoint (PEP) will be updated.

- Secondly, the most recently updated EULAR publication[4] also stresses that the choice of drug should take into account not only the musculoskeletal PsA subtype but also extra (non)- musculoskeletal manifestations related to PsA, including skin psoriasis, uveitis, and inflammatory bowel disease.

  This topic is to some extent covered by the current EMA PsA guideline but could be further highlighted in an updated version.

  It is thus becoming increasingly clear that PsA comprises a number of different clinical domains which manifest their own unique clinical features and immune phenotypes, including arthritis (synovitis), enthesitis, dactylitis, spondylitis, psoriasis and nail disease[12].

- Finally, the most recent EULAR publication[4] includes the following recommendation: 'In patients in sustained remission, tapering of DMARDs may be considered'. The EULAR publication clarifies that tapering means 'dose reduction' not drug discontinuation since the latter usually leads to flares.

  This is not a topic explicitly covered by the existing EMA PsA guideline. The EMA PsA guideline may thus be updated to encourage studies on this topic to better guide use of new PsA treatments over time.

- The EULAR points to consider for the definition of clinical and imaging features suspicious for progression from psoriasis to PsA[5] includes nomenclature that could be relevant for studies looking at PsA prevention / detection of early PsA, or interception with two potential new outcomes in the field of transition: (i) the regression of joint symptoms and imaging features in patients with PsO with subclinical PsA and (ii) reduction of new clinical PsA cases.

  This is a topic not mentioned in the current EMA PsA guideline that could be considered to be included in an updated version.

- In 2020, the ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials[13] came into effect.

  Advice on how the estimand concept is best applied in PsA should be considered for inclusion in the updated guideline.

4. Recommendation

The RIWP of the Committee for Human Medicinal Products (CHMP) recommends revising the Guideline on Clinical Investigation of Medicinal products for the treatment of PsA taking into account the issues identified above.

5. Proposed timetable

Release for consultation on 1 July 2024, deadline for comments 30 September 2024.

6. Resource requirements for preparation

The update of the guideline will involve representatives of the RI-WP, including one Rapporteur. It is anticipated that at least one plenary session discussions at the RI-WP will be needed.

7. Impact assessment (anticipated)

The update of the guideline will have an impact on the clinical development of medicinal products for the treatment of PsA. It will aim to consolidate the current regulatory view on the design of the clinical development programs of these medicinal products and is expected to be helpful to achieve consensus in the evaluation of such products by regulatory authorities.

8. Interested parties

Pharmaceutical Industry, Academia, EU Competent Authorities and patients and health care professional groups. Consultation with other working parties or committees (e.g. SAWP, PDCO) will be initiated, as appropriate.

9. References to literature, guidelines, etc.

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