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

Fields marked with * are mandatory.

* Name of organisation or individual

EFPIA

* Country of organisation or individual

Belgium

* Email

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If you respond on behalf of an organization, please allocate yourself a name abbreviation to be used as "Stakeholder name" in the comment tables below. If you comment as an individual, please ignore this field and use your full name as your "Stakeholder name".

EFPIA

Please click **here** to be redirected to the guideline text. The public consultation is launched on 01 July 2024 until 30 September 2024.

Those participating in the public consultation are asked to please submit comments via the EU Survey tool, by using the specific table for each section. Please note that login is not required to fill in the survey.

Before submission, a draft of the comments can be saved in the EU Survey tool. Once submitted, comments can be edited (by 30 September 2024) by clicking on "Edit contribution" in the link https://ec.europa.eu/eusurvey/ and entering your ID contribution that can be found on the pdf copy of your submission sent via email.

You are invited to provide your organisation or name, country and email address below for the purpose of this public consultation (for further information, please see EMA's Data Protection Statement below).

EMA Privacy Statement

All personal data provided within this survey questionnaire will be processed in accordance with Regulation (EU) 2018/1725 on the protection of individuals regarding the processing of personal data by the Union institutions and bodies on the free movement of such data.

This data protection statement provides details on how the Agency, in its capacity as data controller, will process the information that you have given in your questionnaire.

Internally, an 'Internal Controller' has been appointed to ensure the lawful conduct of this processing operation. The contact details of the Internal Controller are the following: Datacontroller. HumanMedicines@ema.europa.eu

Collection of data

EMA will collect all the personal data in this questionnaire, such as your name, organisation, your view on the topics subject to the survey, country of residence and your contact details. Please do not reveal any other personal data in the free text fields. EMA does not directly intend to collect personal data but to use the aggregated data for the purpose of this survey.

For the collection of data in this survey, EMA relies on the EU Survey external system. For more information on how EU Survey processes personal data, please see: https://ec.europa.eu/eusurvey/home/privacystatement

The EU Survey external system uses:

- Session "cookies" to ensure communication between the client and the server. Therefore, user's browser must be configured to accept "cookies". The cookies disappear once the session has been terminated.
- Local storage to save copies of the inputs of a participant to a survey to have a backup if the server is not available during submission or the user's computer is switched off accidentally or any other cause.
- The local storage contains the IDs of the questions and the draft answers.
- IP of every connection is saved for security reasons for every server request.
- Once a participant has submitted one's answers successfully to the server or has successfully saved a draft on the server, the data is removed from the local storage.

Your consent to the processing of your data

When you submit this questionnaire, you consent that EMA will process your personal data provided in the questionnaire as explained in this data protection statement. You may also withdraw your consent later at any time. However, this will not affect the lawfulness of any data processing carried out before your consent is withdrawn.

Start of data processing

EMA will start processing your personal data as soon as the questionnaire response is received.

Purpose of data processing

The purpose of the present data processing activity is to collect the views of stakeholders and/or concerned individuals in relation to the subject-matter of the survey. Your personal data may be used to contact you in relation to the feedback you have provided in response to the survey. No further processing of your personal data for any other purposes outside the scope of this specific context is envisaged.

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- organisation name (the entity on behalf you respond to this survey)
- or your name (only if you do not respond to the survey on behalf of an organisation)
- your view/comments on the topics concerned

Country information and your email address will not be published.

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You may also lodge a complaint with the European Data Protection Supervisor: edps@edps.europa.eu.

* Please confirm that you have read and understood the Data Protection Statement above and that you consent to the processing of your personal data.
  - (●) Yes
  - ( ) No

* Please confirm that you consent to possibly be contacted by EMA in relation to your survey responses to support the finalisation of the document subject this EU Survey.
  - (●) Yes
  - ( ) No

* Please confirm that you consent to the publication of your organisation name, your name (only if you do not respond to the EU Survey on behalf of an organisation) and your survey responses on the EMA website at the time of issuing the final guideline subject to this survey.

- (●) Yes
- ( ) No

Should you not want to give consent to publish, please send your objections to Datacontroller.HumanMedicines@ema.europa.eu.

Please be aware that the sender of the comments is responsible to not disclose any personal data of third parties in the comments.

When you have filled in the EU Survey, please use the submission button at the end of the form to submit the comments to the European Medicines Agency.

For additional information, please consult EMA's privacy statement.

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1. General comments

	General comment
1	In the context of global development programmes, the alignment of requirements with other regulatory authorities as far as possible is desirable. In particular, in relation to the assessment of efficacy, alignment with other global regulators such as US FDA on the recommendations including the primary endpoint for Phase III registrational trials (see Section 2.3 Discussion, item 2) and clinical trial design elements related to treat to target principles, which has not been endorsed by US FDA historically.
2	Please include considerations on rescue treatments which can be used with/without discontinuing study therapy.
3	Patient population for label: Recent updates to PsA treatment guidelines recommend for some specific disease manifestations to start with a biologic DMARD (bDMARD) rather than requiring failure with a conventional disease-modifying antirheumatic drug (cDMARD) before starting with a bDMARD, e.g. European Alliance of Associations for Rheumatology (EULAR) guideline recommends starting treatment with a bDMARD for PsA patients with predominant axial disease or enthesitis rather than a (cDMARD) (Gossec et al 2024). In addition, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) allows a bDMARD as the first line treatment. Clarification in the guidelines relating to cDMARD failures and patient populations to be studied in clinical trials to support labelling should be provided.
4	While we appreciate an update to the endpoint section, we recommend careful consideration to be given to enable global alignment and use of recognized endpoints in global development programs. Although MDA captures low remission, which is a key endpoint to achieve for PsA, the robustness and global recognition of an endpoint needs to be carefully considered for choosing a primary endpoint. Our rationale for being cautious with choosing MDA as a primary endpoint include (with expanded rationale in responses to Line 67-69, 74-75, and 79): • Lack of comparison to earlier marketed products which do not include MDA in the SmPC • Assessment of subgroups (patients with enthesitis/skin) of the composite MDA response can produce variable results depending on the statistical analysis proposed • Both skin and enthesis can be measured with different assessments (PASI or BSA for skin and LEI or SPARCC or MASES for enthesis) and can produce variable results depending on the assessment • Both skin and enthesis subgroups can vary in subject number between clinical trials, thus increasing

	variability in responses between different studies • To reduce trial complexity, alignment is needed with other key regions/countries for regulatory acceptance of MDA as a primary endpoint • The recognition of a key endpoint such as MDA would be better captured as a required secondary endpoint
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2. Specific comments on text

2.1. Introduction

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	18	In accordance with the following references, we are recommending that the prevalence be 20 to 30%. The Alinaghi (2019) reference used in the Concept paper concludes that 1 in 4 patients with psoriasis have PsA. The point estimates hover around the 20-25% range and vary based on geography/genetics. References supporting 30%: 2014: Mease PJ, Armstrong AW. Managing patients with psoriatic disease: the diagnosis and pharmacologic treatment of psoriatic arthritis in patients with psoriasis. Drugs. 2014 Mar;74(4):423-41. doi: 10.1007/s40265-014-0191-y. https://pubmed.ncbi.nlm.nih.gov/24566842/ 2003: Zachariae H. Prevalence of joint disease in patients with psoriasis: implications for therapy. Am J Clin Dermatol 2003;4: 441–7. https://pubmed.ncbi.nlm.nih.gov/12814334/ 2001: Brockbank JE, Schentag C, Rosen C, Gladman DD. Psoriatic arthritis (PsA) is common among patients with psoriasis and family medical clinic attendees [abstract]. Arthritis Rheum 2001;44(suppl 9):S94.	‘In patients with Plaque Psoriasis (PsO) the prevalence of PsA is approximately 20-30%’
		With regards to the proposed update in general treatment approaches, we would recommend including information with regards to potential risks associated with delaying treatment of PsA.	

2	21-23	Reference: Haroon M, Gallagher P, FitzGerald O. Ann Rheum Dis 2015;74: 1045-1050	Please address potential risks associated with delaying treatment of PsA.
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2.2 Problem statement

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	28-29	In the guideline, EMA should clarify whether 'early' disease detection and treatment constitutes an additional therapeutic goal and therefore a separate target therapeutic indication to the standard indications approved.	
2	38-39	Given the advances in extrapolation and regulatory experience with paediatric approval for PSO, the update of the EMA PsA guideline should reflect when efficacy, safety and PK could be extrapolated from adults to children with PSA after there is an approval of the same therapy in paediatric PSO. In this respect, reference could also be made to ICH E11A Guideline on paediatric extrapolation.	Clarify when efficacy, safety and PK could be extrapolated from adults to children with PSA and reference ICH E11A.
		1. Structural damage: The new guideline should address if the collection of structural damage data for new drugs is mandatory or optional. This is important for the following reasons: • The most critical aspect of evaluating new drugs in PsA is their impact on improvement in clinical manifestation across disease domains and it is very unlikely that the drug which is effective in improvement of clinical manifestation and inflammatory burden will worsen structural damage. In most if not all cases, the reduction in clinical. manifestation/inflammation helps to slow the structural damage progression.	

3		• The standard radiographic methods used to measure structural damage in PsA are not considered fully validated. • Short duration of clinical trials and use of active comparator arms makes the detection of differences in structural damage progression between treatment arms challenging. Some of the drugs approved to treat PsA and considered to be adequate active comparators, have never demonstrated statistically significant or clinically meaningful impact on structural damage in PsA. 2. Strategy and Design of Clinical trials. The guideline should address whether data from Phase 2 dose ranging studies in psoriasis can be extrapolated to psoriatic arthritis given that these conditions are part of the same spectrum of disease, share similar inflammatory pathways and result in similar responses to inhibitors of such pathways. 3. The need for and objectives for active comparator arms.	
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2.3 Discussion (on the problem statement)

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1	42-43	The concept paper covers only limited important development aspects which may need to be updated in the next version of guideline. Examples of topics not included in the concept paper but of high relevance: 1. Structural damage: The new guideline should address if the collection of structural damage data for new drugs is mandatory or optional. This is important for the following reasons: • The most critical aspect of evaluating new drugs in PsA is their impact on improvement in clinical manifestation across disease domains and it is very unlikely that the drug which is effective in improvement of clinical manifestation and inflammatory burden will worsen structural damage. In most if not all cases, the reduction in clinical. manifestation/inflammation helps to slow the structural damage progression. • The standard radiographic methods used to measure structural damage in PsA are not considered fully validated. • Short duration of clinical trials and use of active comparator arms makes the detection of differences in structural damage progression between treatment arms challenging. Some of the drugs approved to treat PsA and considered to be adequate active comparators, have never demonstrated statistically significant or clinically meaningful impact on structural	Consider including aspects relating to structural damage, clinical trial strategy and design, and the need for and objectives of active comparator arms,

		damage in PsA. 2. Strategy and Design of Clinical trials. The guideline should address whether data from Phase 2 dose ranging studies in psoriasis can be extrapolated to psoriatic arthritis given that these conditions are part of the same spectrum of disease, share similar inflammatory pathways and result in similar responses to inhibitors of such pathways. 3. The need for and objectives for active comparator arms.	
2	54 – concomitant study treatment	Should be clear on the wording to clarify concomitant csDMARDs treatment or bDMARDs combination accordingly.	Clarify concomitant study treatment and combination of bDMARDs with csDMARDs
3	55	With regards to potential active comparators in PsA studies, this point needs to be considered carefully in terms of 'imposing' a certain comparator or comparator class. A distinction in terms of treatment positioning needs to be considered where generally 'synthetic DMARDs' are used ahead of biologic options. Therefore, the selection of active comparator should take this into account. Further, as no therapeutic option exists yet for ‘early disease treatment’, the need for active comparator in this setting should not be required.	Clarify the need for active comparator in early disease treatment settings.
		While most of the dosage of the same drug varies between PsO and PsA, Dose ranging studies for PsA	

4	Between 55 and 56	are not robust and are mainly extrapolated from PsO trials. Data on the appropriate dosing for PsA patients is limited and may not accurately reflect the needs of this population. Clear guidance on dose ranging trials for PsA (and PsO) could ensure the most effective dose of medication for these two populations. With the availability of numerous treatment options, it is important to consider the relevant population when designing a clinical trial for PsA. (eg. b/tsDMARD naïve and experienced patients).	Provide clear guidance on dose ranging trials for PsA and PsO. Note the importance of selecting the relevant patient population when designing a clinical trial.
5	66-69	Acknowledge EULAR recommendation and treat-to-target (T2T) approach. However, the translation of T2T principles to the clinical trial context can be challenging e.g. modification of dosing during clinical trials may complicate interpretation of efficacy and safety. See also comments on tapering below.	Note modification of dosing could complicate interpretation of efficacy and safety.
6	66-79	New composite PsA specific endpoints listed in document including MDA will require further research before recommending them in guidelines to use as primary endpoints in pivotal drug development programs. As there is no fully validated composite endpoint measuring PsA activity across all domains, it may be better to continue to use multiple endpoints measuring improvement in individual domains. Even EMA letter of support for MDA from 2022, concluded: Although EMA recognises that MDA has been used in interventional and observational studies in PsA, the performance of MDA as an endpoint in a prospective randomised interventional study is considered as a pending final validation step.	Refer to more research is needed before MDA can be recommended as a primary endpoint.

7	67-69	Aiming for remission or, alternatively, low disease activity through appropriate 'treat-to-target' (T2T) approach, T2T is a treatment strategy in clinical practice. However, adopting such an approach in the context of exploring the properties of a new therapeutic agent is not practical, i.e. one cannot assess the safety and efficacy of a product if the aim is to change treatment regularly. This would significantly impede the assessment of long-term efficacy and safety profile of the new therapy. Assessing the properties of a new agent in a controlled, longitudinal fashion will allow an assessment of the placement of this treatment in a T2T strategy approach.	Note adopting a T2T approach will be challenging in a clinical trial and impacts assessing long-term efficacy and safety.
		While it is worthwhile to consider the evolution of treatment goals in PsA and provide support for MDA as an outcome measure, careful consideration should also be given to historical comparisons. Products currently approved on the market are based on the assessment of either ACR20 or ACR50. Often, MDA was not formally assessed in previous studies so comparison to existing widely used medications may not be possible. While the use of an active comparator in future studies may be considered for this assessment, it would not allow a relative positioning vs other products. In the context of clinical development, the continued use of ACR as a primary endpoint should be envisaged supported with endpoints that measure other clinical manifestations (joint, skin, enthesitis, low disease activity, etc.) as supporting secondary endpoints. The MDA endpoint is a composite endpoint which includes the subgroups of skin psoriasis (BSA/PASI)	

8	74-75	and enthesitis. A number of potential issues arise from this. Firstly, enthesitis can be measured in a variety of ways (e.g. LEI, SPARCC, MASES, etc.) Depending on the enthesitis measure used as part of the composite of MDA, the overall MDA outcome may vary (please also refer to comment on Line 76-78). Secondly, some of the components of the MDA endpoint rely on subpopulations of PsA patients exhibiting certain disease characteristics, such as skin psoriasis or enthesitis. Depending on the size of these subgroups and how the statistical analysis was set up, the level of MDA response could vary widely from study to study, thus making a benchmark or comparisons between therapies difficult. In the 2007 guidance PsARC response is suggested this is now rarely used in registration trials due to high placebo response and lack of recognition my most treating physicians. We would suggest removing the focus on this outcome measure from the guidance.	Note the continued use of ACR as a primary endpoint supported by other relevant endpoints that measure other clinical manifestations.
9	75-79	To assess the efficacy across domains as suggested in the recommendations, outcome assessment per domain and composite outcome measurement of PsA should be standardized based on current evidence. A wide range of domains has been highlighted in OMERACT reflecting the disease involvement in multiple domains and heterogenous impact of the disease on individuals. Ref: The state of the art-psoriatic arthritis outcome assessment in clinical trials and daily practice. Lancet Rheumatol. 2022 Mar;4(3):e220-e228.	Refer to many working groups have evaluated a wide range of domains that are important to understand the impact of disease on individuals.

		Initiating Evaluation of Composite Outcome Measures for Psoriatic Arthritis: 2022 Updates From the GRAPPA-OMERACT Working Group. J Rheumatol. 2023 Nov;50 (Suppl 2):53-57.	
10	76-78	EMA should clarify their intent to amend the methods for assessment of efficacy. In general, endpoints that assess the different manifestations of the disease should be assessed. The guidelines highlight MASES for assessing enthesitis in PsA, however, MASES focuses more on the spinal rather than peripheral manifestations of PsA. Clinical trials of PsA often include LEI for assessment of enthesitis. Recent studies have also included SPARCC for measuring enthesitis. The SPARCC index measures 16 enthesial sites (predominantly peripheral), whereas LEI index measures only 6 sites which are peripheral. SPARCC shows a greater sensitivity and allows detection of a larger subgroup with enthesitis compared to LEI (R.E. N. Granados, 2023). Additionally, a recommendation to study entheseal inflammation via an imaging modality e.g. MRI or US may improve sensitivity of assessment.	Clarify the intent for amending the methods for assessing efficacy.
		We would recommend an update of imaging methods to assess structural damage progression in Phase 2 and Phase 3 studies by adding more sensitive imaging modalities i.e., MRI to assess inflammation and structural damage.	

11	76 to 79	PsAMRIS criteria can be reliably used to assess inflammatory changes suggestive of upcoming structural damage i.e., synovitis, tenosynovitis, periarticular inflammation and bone oedema as well as structural damage i.e., bone proliferation, bone erosions and joint space narrowing. MRI is a non-invasive imaging modality which is more sensitive compared to the use of X-Ray to capture early structural damage progression and allow comparison against placebo in a short period of time, typically over 12-16 weeks. References: 2008: The OMERACT Psoriatic Arthritis Magnetic Resonance Imaging Scoring System (PsAMRIS): Definitions of Key Pathologies, Suggested MRI Sequences, and Preliminary Scoring System for PsA Hands | The Journal of Rheumatology (jrheum.org) The Journal of Rheumatology August 2009, 36 (8) 1816-1824; DOI: https://doi.org/10.3899/jrheum.090352 2014: Validation of the OMERACT Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) for the Hand and Foot in a Randomized Placebo-controlled Trial | The Journal of Rheumatology (jrheum.org) The Journal of Rheumatology December 2015, 42 (12) 2473-2479; DOI: https://doi.org/10.3899/jrheum.141010 2022: Implementation of the OMERACT Psoriatic Arthritis Magnetic Resonance Imaging Scoring System in a randomized phase IIb study of abatacept in psoriatic arthritis Rheumatology, Volume 61, Issue 11,	Please update imaging methods to assess structural damage progression in Phase 2 and Phase 3 studies by adding more sensitive imaging modalities i.e., MRI to assess inflammation and structural damage

		November 2022, Pages 4305–4313, https://doi.org/10.1093/rheumatology/keac073	
12	80-89	Accept the importance of the assessment of other disease domains (e.g. psoriatic nail disease, uveitis and IBD) where appropriate, however assessment in a clinical trial may not be feasible (e.g., mNAPSI) and has not been required for previous drug approvals. Recommend that assessment of these domains may be considered for exploratory analyses but not mandated.	Note assessment of other disease domains may be considered for exploratory analyses and are not mandatory.
13	80-89	Stated in EULAR recommendation: The first extra-MSK manifestation of interest in PsA is skin psoriasis. Although most patients with PsA present with skin psoriasis or have a personal history of skin psoriasis, registry data indicate that many patients with PsA have mild skin involvement. However, even limited skin psoriasis can be troublesome, since relevant skin involvement is defined as either extensive (body surface area involvement >10%), or as important to the patient, that is, negatively impacting their quality of life (such as is the case with face or genital involvement) Current GRAPPA and EULAR recommendations on skin are based on psoriasis literature review. While psoriatic arthritis patient tends to have mild skin involvement, skin efficacy should be included as key measurement to reflect its importance in psoriatic arthritis patients. Currently, endpoint of the trials main focus on joint and have inconsistent skin outcome measurement.	Update text to ‘Secondly, 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.’

		The most recently updated EULAR publication 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. Specifically on skin, clinical recommendation on psoriasis/skin domain has been made based on psoriasis trials due to limited /inconsistent skin data from psoriatic arthritis trials. (Gossec L, Kerschbaumer A, Ferreira RJO, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2023 update Annals of the Rheumatic Diseases 2024;83:706-719)	The choice of drug is to some extent covered by the current EMA PsA guideline but could be further highlighted in an updated version.
14	84-85	The importance of extra-musculoskeletal manifestations is acknowledged. The effect of different therapies on these manifestations can differ. Hence the guidance should clarify what data are required to support future labelling statement related to the effect of therapies on the ESM.	
15	86-89	The concept paper acknowledges the clinical domain in the guidance document Axial inflammation is included as a main disease domain within the guidance and BASDAI > 4 is suggested as a baseline sub pop in which to study response. As the BASDAI is designed to assess efficacy in spinal symptoms for patients with diagnosed inflammatory back pain (axSpA) we propose that the baselines sub populations of any studies population should be more carefully defined by the presence of inflammation by a validated imaging technique i.e. MRI in order to support a label claim for improvement in axial symptoms in PsA patients.	Consider allowing assessment of improvements in axial PsA symptoms using MRI.

16	Between 89 and 90	Current studies primarily focus on assessing disease activity, while both guidelines mention that the goal of treatment is to improve the quality of life. Recommendation to consider including patient-reported outcome assessments for PsA patients, either as a core outcome or as a supplemental benchmark of efficacy could bring the data closer to the goal of treatment. EULAR: The primary goal of treating patients with psoriatic arthritis is to maximise health-related quality of life, through control of symptoms, prevention of structural damage, normalisation of function and social participation; abrogation of inflammation is an important component to achieve these goals (unchanged). GRAPPA: One of the ultimate goals for PsA treatment is to optimize functional status, improve quality of life and wellbeing, and prevent structural damage to the greatest extent possible	Acknowledge guidelines recommend including PROs
		While treat to target approaches are appropriate for clinical practice, they may vary significantly depending on individual patients needs and are not necessarily appropriate for incorporation into clinical trials. If mandated, establishing optimal dose titration to achieve treat-to-target goals may also prolong the time to approval and delay patient access. It is acknowledged that EULAR recommendations state that tapering ‘may be considered’ for patients who are in a state of remission, however this is a Grade B recommendation based on 2b level evidence. Notably,	

17	90-93	there are significant challenges with assessment of tapering in the clinical trial context. Such strategy-type studies are testing both the treatment and the treatment strategy if arms have different rates of dose adjustment. For example, the switching of doses during a clinical trial makes it challenging to attribute adverse events to a given dose, which could make it difficult to determine the relative benefit-risk profile across doses studied. Also, the majority of patients with rheumatic disease require continued therapy on a regimen that has demonstrated efficacy and safety to remain in remission. Many patients have tried treatments and failed to respond. In responders, there is no guarantee that a patient will respond to subsequent re-treatment with the agent for which they have lost response following dose reduction or dose spacing; thus, such an approach may limit treatment options available to a patient. There is also no universally accepted duration of sustained remission or of flare in PsA. All these aspects evidence that the assessment of tapering is not straightforward. Of special concern is that if this type of information / studies were to be requested pre-approval, it would unnecessarily delay treatment access to patients in need of new treatments, as a larger number of patients would need to be studied for a prolonged period of time to select for those who achieve ‘sustained remission’, and then study dose reduction or dose spacing with sufficient time to evaluate for symptom recurrence. This mandate would place sponsors seeking approval of new drug at competitive disadvantage.	Acknowledge there are challenges to incorporate treat to target approaches in clinical trials.
		Suggest update on the section on “Measurement of Structural Joint Damage” and guidance on radiographic	

18	101	imaging methods and endpoints. The use of x-rays only measures damage once it has occurred, not the process which leads to damage. The process leading to damage is important to halt as once damage has occurred it is not reversible. As such, it would be desirable to have specific imaging modalities, such as MRI and CT, incorporated into the guidance for assessment of both progression from PsO to PsA and also as a measure of radiographic progression.	Refer to using specific imaging modalities such as MRI and CT to assess radiographic progression.
19	105-108	Consideration should be given to the 4 elements of an estimand (population, outcome, summary measure and intercurrent events) and these should be clearly explained in the statistical analysis plan. While the first 3 are generally straight-forward, specific attention should be given to what should be defined as an intercurrent event and how these should be handled. Examples would include discontinuation due to adverse events or lack of efficacy as well as study specific items such as the subjects who start rescue medication before the timepoint being summarized. A hypothetical example estimand structure is detailed below for a primary endpoint of ACR50 at Week 24: Population: Subjects enrolled according to protocol-specified inclusion/exclusion criteria and randomized to IMP Subject-level outcome: ACR50 at Week 24 Intercurrent event handling: Intercurrent events are defined as having a discontinuation due to adverse event or lack of efficacy as well as receiving rescue medication prior to Week 24. Subjects with intercurrent events of discontinuation due to adverse event or lack	Include more details relating to estimand considerations in particular intercurrent events and strategies for addressing them.

		of efficacy will be set to non-responder after discontinuation. For subjects starting rescue medication, data following the event will be set to missing and the ACR50 components will be imputed using multiple imputation and ACR50 recalculated on the imputed data. Missing data due to any other reason will be set to non-response. Population-level summary measure: Conditional odds ratio comparing active treatment to placebo. Further, sensitivities should be considered for hierarchical endpoints such as reference-based imputation when standard multiple imputation is used, or by applying general non-responder imputation if the outcome is binary/categorical.	
20	Section 3	As a consideration for assessment of the HRQoL, we would recommend inclusion of PsAID-12 as a disease specific measure of disease impact in PsA. The measure has been developed in PsA to capture PsA core symptoms (including pain, fatigue, and skin symptoms) and impact on HRQoL relevant to individuals living with PsA. In 2018, the endpoint PsAID12 was provisionally endorsed as core outcome measure for disease-specific HRQOL in PsA clinical trials by GRAPPA-OMERACT PsA working group but was missing evidence of psychometric performance. Recently, the PsAID-12 underwent a robust psychometric validation analysis which demonstrated the PsAID-12 is reliable, valid, and responsive to change, making the PsAID-12 fully fit-for-purpose to capture HRQoL in clinical trials in PsA.	Consider other disease specific measures to assess disease impact such as PsAID-12.

		Assessment could be further aligned to the OMERACT core set with inclusion of Fatigue and Pain measures.	
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2.4 Recommendation

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
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2.5 Proposed timetable

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
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2.6 Resource requirements for preparation

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
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2.7 Impact assessment (anticipated)

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
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2.8 Interested parties

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1	124-126	It is recommended that expertise on real world evidence also be included in relation to extrapolation of paediatric data (see comment above)	Pharmaceutical Industry, Academia, EU Competent Authorities and patients and health care professional groups. Consultation with other working parties or committees (e.g. SAWP, PDCO), including real world evidence expertise, will be initiated, as appropriate.
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2.9 References to literature, guidelines, etc.

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
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Other comments

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1			
2			
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Thank you for your contribution.

Contact

Contact Form