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Guideline on clinical investigation of medicinal products for the treatment of psoriatic arthritis

Draft

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This guideline replaces 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.

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Guideline on clinical investigation of medicinal products for the treatment of psoriatic arthritis

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Executive summary

This document is a revision of the 'Guideline on clinical investigation of medicinal products for the treatment of psoriatic arthritis' (CHMP/EWP/438/04), which came into effect in July 2007. The current revision has considered that clinical practice has been subject to significant evolution since publication of the previous guideline.

Relevant treatment goals, general design of clinical studies, definition of study population, and study endpoints in terms of efficacy and safety were updated in the light of the currently available treatment options for psoriatic arthritis (PsA).

1. Introduction (background)

PsA is a multifactorial, chronic inflammatory arthropathy of the peripheral and axial joints affecting synovium, tendons, entheses, skin, and bone, which imposes a significant burden on patients. To prevent joint damage from persisting inflammation, diagnosis and treatment without delay is advocated. In patients with psoriasis, the prevalence of PsA is approximately 20-30% [1-5]; in some PsA patients, arthritis and psoriasis occur simultaneously or PsA precedes skin disease [6].

Non-steroidal anti-inflammatory drugs (NSAIDs) and local injections of glucocorticoids can be used as short-term symptomatic treatment, however in patients with polyarthritis or mono-/oligoarthritis and poor prognostic factors, a conventional synthetic disease-modifying antirheumatic drug (csDMARD) such as methotrexate, should rapidly be initiated. According to currently prevailing clinical guidelines, patients with inadequate response to at least one csDMARD should receive a biological disease-modifying antirheumatic drug (bDMARD, targeting e.g., Tumor Necrosis Factor alpha (TNFα), Interleukin (IL)-17, IL-23)) or targeted synthetic disease-modifying antirheumatic drug (tsDMARD, e.g., Janus Kinase Inhibitor (JAKi)) [7]. Current treatment guidelines provide guidance on the appropriate use of the different therapeutic options in the presence of different musculoskeletal and/or extra-musculoskeletal manifestations, including treatment algorithms in case of non-response [7].

Despite the number of existing treatment options for PsA, a medical need still exists for patients with inadequate response or intolerance to currently available therapies.

2. Scope

Guidance is provided on the clinical development and evaluation of medicinal products intended for the treatment of the adult form of PsA including general treatment goals, target patients, overall design and methodology of clinical studies in PsA, endpoints selection as well as safety aspects.

The paediatric form of PsA is addressed by the 'Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis' (EMA/CHMP/239770/2014 Rev.2).

3. Legal basis and relevant guidelines

This Guideline should be read in conjunction with the introduction and general principles of Annex I to Directive 2001/83/EC, as amended, and all other relevant European Union (EU) and ICH guidelines. These include, but are not limited to:

- Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02 corr)

- Guideline on Clinical Investigation of Medicinal Products for the treatment of Juvenile Idiopathic Arthritis (EMA/CHMP/239770/2014 Rev. 2.)
- Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis (EMA/CPMP/EWP/4891/03 Rev.1, Corr 1*)
- The Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95; ICH E1A)
- Note for Guidance on Studies in Support of Special populations: Geriatrics (CPMP/ICH/379/95; ICH E7)
- Guideline on drug interaction studies (EMA/CHMP/ICH/652460/2022; ICH M12)
- Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1)
- Guideline on Adjustment for Baseline Covariates in Clinical Trials (EMA/CHMP/295050/2013)
- Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96; ICH E9)
- Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (EMA/CHMP/ICH/436221/2017; ICH E9 (R1))
- Note for Guidance on choice of Control Group in Clinical Trials (CPMP/ICH/364/96; ICH E10)
- Dose-Response Information to Support Drug Registration (CPMP/ICH/378/95; ICH E4),
- Guideline on General Principles for Planning and Design of Multi-Regional Clinical Trials (EMA/CHMP/ICH/453276/2016 Rev.1; ICH E17)
- Guideline on General principles for model-informed drug development (EMA/CHMP/ICH/496426/2024; ICH M15)

4. Patient selection

Patients selected for inclusion in clinical PsA studies, should be diagnosed and classified according to internationally established criteria such as the Classification Criteria for Psoriatic Arthritis (CASPAR) [8], with symptom onset normally expected at least 6 months prior to screening. This applies unless there is a specific study objective to detect and treat early, which would require special considerations and definitions e.g. pre-clinical (subclinical) PsA and very early PsA [9].

To meet the CASPAR criteria for PsA, a patient must have inflammatory articular disease (joint, spine, or entheseal) and score ≥3 points among psoriasis (current or personal/family history), psoriatic nail dystrophy, negative rheumatoid factor (RF), dactylitis (current or history), and radiologic evidence of juxta-articular new bone formation. The CASPAR criteria are currently widely used in clinical studies for PsA [e.g. 10, 11]. These criteria allow classification of subjects without psoriasis and / or with positive RF, provided they have other key features of the disease. However, current or previous psoriasis is anticipated to be part of the eligibility criteria in the clinical study unless duly justified.

The predominant clinical phenotype (polyarthritis with or without dactylitis, mono-/oligoarthritis, enthesitis, axial disease, and/or skin or nail disease) is considered crucial for the treatment choice [7, 9] and is also an essential aspect of patient eligibility for PsA studies. This is particularly relevant for axial involvement which should normally be considered as part of the eligibility criteria, if a broad indication is targeted. In any case, the study population to be included in clinical studies should support the claimed therapeutic indication.

Demographic characteristics of study patients should be well documented.

PsA disease characteristics, including the duration, severity, extent, activity of the underlying disease (both for the arthritis and the skin psoriasis), other relevant medical history and previous and concomitant therapy should be well documented as potential effect modifiers.

Relevant identified sub-populations should be justified and defined *a priori* in the study protocol and if specific analyses are foreseen, these sub-populations should be considered as stratification factors in randomisation as well as adequate sample size.

Moreover, patient data on extra-musculoskeletal manifestations (e.g. skin psoriasis, uveitis, inflammatory bowel disease) and comorbidities (e.g. obesity, metabolic syndrome, cardiovascular disease, depression) should be carefully collected.

Disease activity at study inclusion should be assessed by means of validated scales and considering several aspects of the disease such as pain and/or swelling (see section 5.2). In general, patients with moderate to severe disease activity should be included to enable demonstration of sufficient treatment response. This applies to studies aiming to establish proof of concept or select dose as well as confirmatory studies. The recommendation is applicable unless there is a specific objective for the claimed therapeutic indication to target a population of subjects with low disease activity at baseline. Disease activity at time of enrolment in the clinical studies should be distinguished from the level of already present structural damage to the joint and the functional (dis)ability associated with this damage. These two aspects should be documented separately.

Patients included in clinical studies would normally be expected to have active PsA as measured by the number of swollen and tender/painful joints (American College of Rheumatology (ACR) joint count):

- For the peripheral disease activity, in order to enable demonstration of a sufficient treatment response, the patients should preferably have ≥3 swollen joints and ≥3 tender joints. In case slowing of radiographic progression is targeted, it is recommended that at least one erosion in hand/foot and elevated serum level of C-reactive protein (CRP) is present at time of enrolment.

- Axial disease activity may be assessed through composite scales such as the Ankylosing Spondylitis Disease Activity Score (ASDAS) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) complemented with either the measurement of individual symptoms (e.g. pain) and/or global patient assessments of the disease with visual analogue scales (VAS). Moderate to severe axial disease baseline activity is recommended in order to show a sufficient treatment response (e.g. ASDAS ≥2.1 or BASDAI ≥4 and nocturnal/spinal pain as measured by either VAS ≥4 cm or numerical rating scale (NRS) ≥4 at baseline); also see 'Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis' (EMA/CPMP/EWP/4891/03 Rev.1, Corr 1*). If active axial disease is not part of the eligibility criteria, predominantly patients with a peripheral phenotype are likely to be enrolled and this may require reflection in the product information.

The plain radiograph is the standard imaging technique used for PsA, however additional imaging techniques (e.g. Magnetic Resonance Imaging (MRI), computed tomography (CT), or ultrasound) may be used (see sections 5 and 7).

A minimum duration of active disease should be established before entering the study. At least 3 months of active disease is expected when assessing medicinal products to be used in patients not controlled with NSAIDs [8]. The lack of response to appropriate doses of NSAIDs based on generally agreed recommendations at the clinical practice level should be well documented.

Biologic measures of inflammation (i.e. erythrocyte sedimentation rate (ESR) and CRP) should be recorded at study baseline since these have been associated with progression of joint disease [12, 13]. Activity of the skin lesions, when present, should also be assessed using available validated tools for

psoriasis; also see 'Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis' (CHMP/EWP/2454/02 corr).

Regarding patient selection for confirmatory studies, including previous treatment approach, see further in section 6.2.2 below.

5. Assessment of efficacy

5.1. Efficacy criteria/treatment goals

Assessment of treatment effects should cover the relevant disease domains established for PsA, reflecting the complex and heterogeneous nature of the disease. These include assessment of peripheral arthritis, enthesitis, dactylitis, axial disease, structural damage, skin and nail involvement, as well as the evaluation of quality of life (QoL).

From a regulatory perspective, the following goals of treatment can be defined:

1) Improvement and control of PsA symptoms across disease domains

2) Improvement of physical function

3) Slowing or prevention of structural damage

4) Improvement and control of inflammation

5) Overall improvement in QoL

As for other rheumatologic diseases, the treat-to-target (T2T) approach applies to PsA in current clinical practice. Treatments should thus be aimed at achieving the target of remission, corresponding to an abrogation of overall inflammation. If remission is not achievable, low disease activity may be used as an alternative target [7].

Although still not an established approach within this field, for studies looking at PsA prevention or interception, objectives may include the regression of joint symptoms and imaging features in patients with psoriasis with subclinical PsA as well as reduction of new clinical PsA cases [9].

5.2. Methods to assess efficacy criteria

Core domains to assess the efficacy of medicinal products for PsA have been established together with specific scoring methods to evaluate differences in these domains [14-16].

Main domains to be assessed in PsA and instruments to be used in each domain

<u>Musculoskeletal Disease activity</u>

- Peripheral Joint Assessment

Assessment of PsA disease activity in the joints is commonly made by the ACR joint count. The ACR joint count documents the number of joints with joint-line tenderness, stress pain, and/or swelling. Since the pattern of peripheral joint involvement in PsA is clearly different to that of rheumatoid arthritis (RA), increased joint counts to cover distal interphalangeal joints of the hands and both proximal and distal interphalangeal joints of the feet should be used (e.g. the 68/66-joint graded assessment of tenderness/swelling; 78/76-joint graded assessment of tenderness/swelling). Dactylitis, whenever present, should be counted as one active joint. Although not specifically developed for PsA,

the appropriately modified ACR joint count has been demonstrated to be a reliable measure of joint disease activity in PsA.

Different response criteria based on the extent of symptom improvement (ACR20, 50, or 70) can be used. The ACR20 criteria requires a ≥ 20% reduction in the tender joint count, a ≥ 20% reduction in the swollen joint count and a ≥ 20% reduction in 3 of 5 additional measures: a) patient assessment of pain, b) patient global assessment of disease activity, c) physician global assessment of disease (PGA) activity, d) disability index of the health assessment questionnaire (HAQ) and, e) acute phase reactant. Analyses of ACR50 and ACR70 include the same criteria as ACR20, with the use of a higher percentage improvement (50% and 70%) instead of 20%.

Measures specifically developed for the use in PsA include the Disease Activity index for Psoriatic Arthritis (DAPSA) [17]. Along with a 66/68 joint count, the DAPSA also includes evaluation of patient's pain and CRP levels. It is calculated by summing the following components: Tender Joint Count (TJC) 68, Swollen Joint Count (SJC) 66, Patient Global Assessment (PtGA), Patient Pain Assessment on a 10cm VAS, and CRP in mg/dL. The clinical DAPSA (c-DAPSA), which omits CRP, has also been used as an alternative [18-19]. It can be useful if the medicinal product is known or expected to interfere with signalling by acute phase reactants such as CRP.

Another disease-specific measure is the Psoriatic Arthritis Response Criteria (PsARC) [20] where a response is defined as at least 2 of 4 parameters to be fulfilled: 30% reduction in the SJC, 30% reduction in the TJC, improvement by at least one point in Patient Global Assessment or Physician Global Assessment on a 0–5 Likert scale.

Joint Disease Activity has also been evaluated as part of more comprehensive composite measures such as the Minimal Disease Activity (MDA) [21] and Psoriatic Arthritis Disease Activity Score (PASDAS) [22]. Both scores include Tender Joint and Swollen Joint Counts together with the combined evaluation of other relevant disease domains (e.g. MDA includes skin assessment while PASDAS includes dactylitis). While the MDA is a binary outcome aimed to characterise a state of disease activity that is close to remission, the PASDAS is a continuous measure with a weighted calculation of all included components with a maximum score of 11 reflecting different states of disease activity.

- Enthesitis

Different clinical enthesitis indices, borrowed from ankylosing spondylitis (AS) with primary focus on axial sites, had been initially developed for PsA (e.g. the Mander Index and the Maastricht Ankylosing Spondylitis Enthesitis (MASES) Index). These scores may not be the most suitable for clinical studies in PsA due to limited evaluation of peripheral entheseal sites which are more common in PsA [23]. More specific measures have thus been developed (e.g. the Leeds Enthesitis Index (LEI) and the Spondyloarthritis Research Consortium of Canada (SPARCC) Index) that are both based on the evaluation of tenderness after applying pressure to enthesial sites of interests. Data on validation of LEI and SPARCC are however currently limited while reliability and correlation with other enthesitis indices could be shown [24].

- Dactylitis

The most commonly used measures to evaluate dactylitis include a simple dactylitis count, the dactylitis severity score (DSS) with a range from 0 to 60 and the Leeds Dactylitis Index (LDI) ranging from 0-6.

- Axial Symptoms

Measures of axial symptom activity developed for AS (e.g. the BASDAI or the ASDAS) might be used to assess the effect on PsA axial activity. A recent report suggests that both tools can assess axial

symptoms relatively independently of peripheral disease activity [25]. Nevertheless, clear data on specificity for axial involvement is still limited.

Measure of physical function

The assessment of physical function by patient-reported outcomes measures is the preferable approach. The Health Assessment Questionnaire-Disability Index (HAQ-DI) is widely used in clinical studies with PsA. The HAQ-DI was originally developed for RA and adapted for arthritic conditions in general. It assesses patient's ability to perform various daily activities. Other modified HAQ versions include the HAQ-Spondyloarthritis or the modified health assessment questionnaire (mHAQ) [26].

Measure of Structural Joint Damage

Inhibiting the progression of joint damage is a key goal of therapy. The most frequently involved joints are those in the hands and wrists, followed by the feet. In general, the radiographic features can be grouped into destructive and proliferative changes. Erosions are a typical destructive feature that may lead to the characteristic pencil in cup phenomenon.

Conventional radiographs have been widely used in the past to assess the extent of damage in clinical studies for PsA, and several semiquantitative scoring systems, originally developed for use in RA, have been modified to assess structural damage progression in PsA [27]. These include the modified Sharp score, the Sharp–Van der Heijde modified scoring method and a modified Steinbrocker scoring method. A radiographic method specifically developed for PsA is the Psoriatic Arthritis Ratingen Score (PARS). It evaluates both destruction and proliferation in 40 joints of the hands and feet. These, and further not explicitly mentioned methods, require further clinical validation.

The scoring methods developed for use in AS can be applied to assess the spine and sacroiliac joint abnormalities in PsA, since features might be indistinguishable with the exception of the characteristic presence of paramarginal syndesmophytes and asymmetry. Validated methods are the Bath Ankylosing Spondylitis Radiology Index (BASRI), the Stoke Ankylosing Spondylitis Spine Score (SASSS), and the modified SASSS.

Other scoring methods using additional imaging techniques (e.g. MRI, CT or ultrasound) may be used for joint damage evaluation as they can provide a more sensitive measure for capturing early changes in structural damage progression. As regards to MRI assessment, the outcome measures in RA clinical studies (OMERACT) group developed the Psoriatic Arthritis Magnetic Resonance Image Scoring System (PsAMRIS). This method scores synovitis, edema, tenosynovitis, periarticular inflammation, erosion, and bone proliferation [28].

The choice of the method and features to be assessed should be predefined and justified. Unless the chosen method is well established based on its previous use in clinical studies, support that it is sufficiently validated and fit for the purpose should be provided at the time of dossier submission.

Other domains and instruments to be assessed

- Skin disease activity

Demonstration of efficacy on psoriatic skin disease will require separate specific studies. Nevertheless, some patients will suffer from skin disease at the beginning or during the study. The effect of any new therapy for PsA on skin lesions should thus be assessed.

Different validated scoring methods to assess skin or nail lesions are available. Selection should consider the form of psoriasis, the body surface area involved, and the presence of nail lesions.

For the assessment of nail symptoms, Nail Psoriasis Severity Index (NAPSI) or it's modified version (mNAPSI) which includes a more simplified assessment are available. Other measurements include the Global Assessment of Fingernail Psoriasis (PGA-F).

Also see the 'Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis' (CHMP/EWP/2454/02 corr) which includes recommendations for the assessment of the effect on skin lesions.

- Biological measures of inflammation

Levels of CRP or the ESR may be related to the activity of the disease. Please refer to section 6.1.2 for further comments on PD markers.

- Additional patient-reported outcomes including QoL

Patient-reported outcome measurements to evaluate the QoL can be valuable tools to assess the disease activity from a patient's perspective. Evaluation may be conducted using disease-specific instruments and/or generic instruments.

Available disease-specific instruments include but are not limited to the Psoriatic Arthritis Quality of Life (PsAQoL) and the psoriatic arthritis impact of disease (PsAID) scores. The PsAQoL covers various aspects including physical, emotional, and social impacts as well as fatigue and depression but does not specifically capture pain, anxiety and skin symptoms which are also included in PsAID score. Generic instruments include the 36-item short form survey (SF-36) for HRQoL, the VAS for pain evaluation, or the functional assessment of chronic illness therapy - fatigue (FACIT-F) to assess fatigue.

Multidimensional scales assessing QoL may provide complementary information to that from the main variables and not only that related to the improvement of symptoms and physical function. The effect of arthritis and psoriasis on health-related QoL should be assessed independently.

If the chosen method is not well established based on its previous use in clinical studies, support that it is sufficiently validated should be provided at the time of dossier submission.

- Global assessment

Patient and/or physician's subjective perception are important complementary variables that may be measured, by means of a VAS, to inform on global status during a recent past period.

6. Study design

6.1. Pharmacology studies

6.1.1. Pharmacokinetics

The Pharmacokinetic (PK) properties of the medicinal product should be thoroughly investigated in accordance with relevant guidelines.

6.1.2. Pharmacodynamics

The pathophysiology of PsA is characterised by the complexity of an activated immune system with multiple cellular pathways involved, which are dynamic in the different stages or presentations of the disease and in the distinct tissues involved. Many cytokines contribute to the inflammation of the skin and joints in patients with PsA (e.g., TNFα, IL-17, IL-23) [1, 29, 30]. High-sensitivity CRP (hs-CRP),

ESR, or serum amyloid A (SAA) are generally correlated with inflammatory responses. Depending on the specific target of the medicinal product under development, pharmacodynamics (PD) endpoints will have to be selected accordingly.

6.1.3. Interactions

Interaction studies should be performed in accordance with current guidelines (see Guideline on drug interaction studies (EMA/CHMP/ICH/652460/2022; ICH M12)). Evaluation of any interaction potential should be performed with medicinal products likely to be co-administered in clinical practice or planned to be co-administered during clinical studies (e.g., csDMARDS). The need for conducting interaction studies should be based on the known PK and PD properties of the medicinal product.

6.2. Therapeutic studies

6.2.1. Exploratory and dose finding studies

The included population in exploratory studies should inform on the target population of the pivotal study(ies) (see section 6.2.2).

An appropriate dose finding study in patients with PsA is recommended to find the posology regimen with the most favourable benefit-risk ratio.

There is uncertainty that PsA and psoriasis or other arthropathic diseases respond in a similar way to the same dosage. Therefore, dose guidance provided by previous studies in other related conditions may be of limited value although in exceptional cases, extrapolation of dose finding data could be possible if based on solid evidence and well justified.

A minimum effective dose should be established. In addition, efforts should be undertaken to explore different doses or intervals according to the respective patient characteristics (i.e. disease severity, inflammation, special populations in need of lower doses) as well as to define the need for weight adjustment or adjustment to other co-variates.

To describe exposure-response relationships, the development of appropriate population PK-PD models is recommended taking the general principles for model-informed drug development into account (see General principles for model-informed drug development; ICH M15).

For dose finding, placebo controlled parallel group studies are recommended. Study duration should be adapted to the expected onset of treatment effect (e.g., 12-24 weeks). ACR20 or ACR50 may be appropriate measures for a dose finding study.

6.2.2. Confirmatory studies

The effect of the medicinal product on symptoms and physical function should be demonstrated in patients affected by PsA. Depending on the mode of action of the medicinal product, any potential effect on slowing or prevention of structural damage (i.e., disease modifying effect) should additionally be explored, based on radiological evidence. Although collection of structural damage data may not be strictly mandatory for approval of a new medicinal product intended for the treatment of PsA, data on whether there are any signals suggestive of structural worsening are expected to be provided. The approach outlined below ("Additional claim to prevent structural damage") is likely the most straight forward option for generating this data, but alternative approaches are acceptable as well, if they result in an equal amount of robust data.

Study treatments

For demonstrating efficacy of a new PsA treatment, it is recommended to show superiority to placebo. For demonstrating short term efficacy, a placebo-control study should be feasible.

It is recommended to also include an accepted active comparator to contextualise the measured differences from placebo and to facilitate an evaluation of the effect size and clinical relevance of those differences. In addition, inclusion of an active comparator will support the benefit-risk assessment of long-term maintenance of effect, which for ethical reasons, is usually not feasible to be investigated using a placebo-control. Further, the study may include elements of re-randomisation of subjects in the placebo arm to either the new treatment or the active control arm after assessment of short-term efficacy.

Demonstration of superiority of the active comparator versus placebo serves as a confirmation of the sensitivity of the clinical setting. It is usually not necessary to formally demonstrate non-inferiority to the active comparator but estimates of treatment effect differences between the active comparator and the new medicinal product should preferably be reported with confidence intervals. The choice of an active comparator as well as its dose should be adequately justified according to the target population and target indication, the envisaged place of the product under evaluation in the treatment algorithm and conventions of clinical practice. Posology, mode of action, time to onset of efficacy, duration of action and safety aspects of the active comparator should also be considered.

Clinical studies aiming to show superior efficacy to an active comparator are acceptable but even in this case it is preferrable to include a placebo arm to evaluate the absolute efficacy and safety profile of the medicinal product.

In DMARD-naive patients intolerant or non-responsive to NSAIDs, methotrexate may be an appropriate active comparator (as it is currently standard of care for these patients, please refer to current treatment guidelines [7]).

If DMARD-inadequate responders (e.g., csDMARD or bDMARD) are selected as target population, clinical studies could be designed as add-on studies on top of adequate concomitant 'standard of care', (e.g., methotrexate). As currently there are numerous DMARD-treatment options available, efforts should be undertaken to select an appropriate active comparator also in these target populations.

The concomitant standard therapy should be in line with applicable treatment guidelines, carefully documented, and its impact on results analysed based on a pre-established plan. Also, the previous use and response to standard therapy should be documented.

Appropriate criteria for rescue treatment, especially in long-term studies, should be defined and the choice of rescue medication should be aligned with clinical guidelines [7], see also below in 'intercurrent events'.

In line with T2T approaches and recent treatment guidelines [7], for patients in sustained remission regarding core domains of the disease, tapering of DMARDs i.e. dose reduction may be considered. Studies analysing this topic are encouraged to better guide the use of new PsA treatments over time. These types of studies may be conducted pre-approval or planned to be conducted post-approval.

Patient selection/target population

The choice of the target population of the clinical study and the to be included population will depend on the characteristics of the medicinal product (i.e. mechanism of action, expected safety profile) and on the intended therapeutic indication. Baseline information on all relevant efficacy and safety parameters should be collected before start of the study treatment and over an appropriate period of

time, depending on the parameter and endpoint. General aspects on patient selection are described in section 4.

Potential target populations could consist of:

- patients with no previous DMARDs treatment history (i.e., DMARD-naive) and an inadequate response or intolerance/contraindication to NSAIDs
- patients with no previous bDMARDs treatment history (i.e., bDMARD-naive) and an inadequate response or intolerance/ contraindication to previous csDMARDs treatments (e.g. methotrexate), or
- bDMARD treatment-experienced patients with inadequate response or intolerance/ contraindication to at least one prior biologic agent.

The inadequate response to previous treatment should be well documented ideally considering criteria reflecting appropriate dosage and duration of treatment.

Separate clinical studies are the recommended approach to demonstrate efficacy and safety for target populations that differ in terms of previous treatment (e.g., newly diagnosed, bDMARD-naïve or bDMARD treatment-experienced patients) as underlying treatments are diverging and different active controls would be needed. If included in a single pivotal study, the study, its statistical analysis and sample size would need to be carefully planned to allow an assessment of consistency of effect across these important subgroups.

In general, subgroup analyses accounting for known prognostic factors (some of which will be stratification factors in the randomisation) should be predefined in the study protocol, to allow examining consistency of effect.

Choice of endpoints

As described above (see section 5.2), several specific measures have been developed to assess the different disease manifestations in PsA providing a suitable framework to evaluate the efficacy of medicinal products throughout the whole symptomatic spectrum of the disease. In general, endpoints intended to be the basis for claims in the product information should be adequately validated for this purpose.

Depending on the nature of the medicinal product and the expected onset of effect, pivotal efficacy may be demonstrated after 12 - 24 weeks study duration.

While the choice of primary and secondary endpoints ultimately depends on the specific aspects of PsA being targeted by the medicinal product under investigation, the following general recommendations can be made:

Primary endpoints for medicinal products intended to improve symptoms/physical function

Joint inflammation is the key feature of PsA and changes in joint activity should be evaluated as part of the primary efficacy endpoint.

Two main responder criteria have been used in clinical studies for PsA: the ACR response criteria and the PsARC.

The ACR20/50/70 response criteria originally developed for RA, have been widely adopted and used in clinical studies for PsA. The ACR20 response criteria have been used as the primary or secondary endpoint in previous clinical studies in PsA. Selecting the ACR20 as the primary and ACR50/70 as secondary endpoint can be an acceptable approach for clinical studies in PsA. Still, using ACR50 as a

more stringent primary endpoint should be considered as this reflects a more meaningful treatment response.

The PsARC have been evaluated in many clinical studies in PsA up to now and it is also considered an acceptable primary endpoint.

These response criteria may discriminate well between effective treatment and placebo. However, they focus on peripheral polyarticular form of PsA and thus, many of the proposed core outcomes such as spondylitis and features such as dactylitis and enthesitis are not incorporated. Consequently, the relevant features lacking in primary composite endpoints should be separately addressed, e.g. through additional assessment as secondary endpoints.

In the rare cases where a predominant axial involvement exists, the 'Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis' (EMA/CPMP/EWP/4891/03 Rev.1, Corr 1*) should be followed.

As more effective therapies become available for PsA, disease remission is increasingly regarded as an appropriate therapeutic goal. Treatment should thus be aimed at reaching the target of remission or, alternatively, minimal/low disease activity, by regular disease activity assessment and appropriate adjustment of therapy. Consequently, while the above-mentioned response criteria based on joint disease activity can be an acceptable primary endpoint for clinical studies in PsA, it should be accompanied by appropriate and statistically high-ranked secondary endpoints that reflect the T2T approach. The DAPSA, the MDA or other existing or yet to be defined measures may be considered, provided that sufficient data on validation in the context of T2T are available.

For these responder endpoints, treatments should be compared with the difference in response rate as the summary measure.

Additional claim to prevent structural damage

Several radiological scoring systems have been established for the use in PsA but further validation is still needed. At present, the choice of the method should be justified and joints and features to be assessed as well as the minimum relevant change should be pre-specified.

Radiographs should be taken on fixed and predefined time points and be assessed by at least two assessors blinded for the allocation of the patient to type of treatment, chronological sequence of the radiographs and initial assessment(s) of the other assessor(s). The method for obtaining the final score should be described in detail (e.g. consensus) and be predefined. Handling of missing information should be described and justified.

Even if the claim for prevention of structural damage may not be sought, structural changes are still recommended to be measured in the development program (e.g. as secondary endpoints in one of the confirmatory studies or a separate study) to provide reassurance that there is no deleterious effect, e.g. deterioration of structural damage caused by the product. In general, the mode of action and the available safety data should be considered during the planning of structural damage endpoints.

The section "Study treatments" (see above) includes considerations on comparators in studies evaluating long-term effects.

Other more sensitive imaging methods, such as MRI, that allow an earlier evaluation of structural damage progression may be considered as endpoint if supported by adequate validation.

Secondary endpoints

Axial involvement

Axial involvement should be assessed as an important secondary endpoint. In general, efficacy on both peripheral and axial arthritis should be separately demonstrated in order to gain a broad indication in PsA. Morning stiffness, spinal and nocturnal pain as well as physical function should preferably be evaluated. The Assessment in Spondylo Arthritis International Society (ASAS) Response Criteria has been used to measure efficacy on the symptoms of AS and can be considered a valid composite measure of efficacy in axial arthritis in PsA. The ASAS20 is defined as an improvement of at least 20% and absolute improvement of at least 10 units on a 0-100 mm scale in at least 3 of the following domains: patient global assessment, pain assessment, function, and morning stiffness. Absence of deterioration in the remaining domains should be documented. Analyses of ASAS40 includes the same criteria but with the use of a higher percentage of improvement (40%). Additional measures that can be included for axial disease evaluation include the BASDAI and/or the ASDAS score.

Please refer to the 'Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis (EMA/CPMP/EWP/4891/03 Rev.1, Corr 1*)' for recommendations on which outcome measure to use for axial involvement.

Skin lesions

From the patient's perspective PsA and psoriasis are likely seen as different manifestations of the same condition. Therefore, the impact of any treatment aimed for PsA should include a skin assessment. In the assessment of the effect on skin lesions, the 'Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis' (CHMP/EWP/2454/02 corr) should be followed.

However, when selecting between the available methods it should be considered that assessment instruments designed for psoriasis studies may not be appropriate for PsA studies, since participants are selected based on musculoskeletal disease and may have minimal skin disease. Skin evaluation may be performed in a subgroup with sufficient skin involvement (e.g. >3% affected body surface area (BSA)), while data for complement subgroup and the total population should also be assessed.

Other secondary endpoints

Other secondary endpoints should include evaluation of additional symptomatic features of PsA not covered by the endpoints described above including dactylitis and enthesitis.

Individual components of composite instruments should be presented. Other composite criteria not assessed as primary endpoints, as well as individual assessments of the main domains of the disease may also be evaluated.

Additional endpoints may also be the different percentages of improvement for each composite endpoint not included as primary outcome.

Further, inclusion of relevant patient-reported outcome measures capturing the impact of QoL (see section 5.2) either as secondary or exploratory endpoint is recommended.

Intercurrent events

For short-term outcomes, treatment discontinuation is considered as treatment failure, and a *composite strategy* is of most regulatory interest. For the above-described responder endpoints, it is expected that study participants that discontinue the assigned treatment are considered as non-responders.

For radiographic endpoints, a *treatment policy strategy* is of most regulatory interest for handling 'treatment discontinuation', which means that the radiographic outcome is of interest regardless of

discontinuation. Correspondingly, efforts should be made to maintain participants that discontinue treatment in the clinical study to continue the outcome collection.

In many studies, concomitant medications for PsA (e.g., csDMARDs or NSAIDs) can be initiated, or its dose increased, in response to lack of improvement of the participant's outcome based on defined criteria (e.g. less than X% improvement in a defined endpoint at week 12 after treatment initiation). Different wordings have been used to describe this practice (use of rescue medication, early escape criteria, inadequate responders), which will be termed 'initiation of rescue medication' in the following. For confirmatory clinical studies, the initiation of rescue medication indicates a relevant (negative) outcome on its own and should be handled with a *composite strategy*. For the responder endpoints described above, participants that initiate rescue medication should be categorised as non-responders. Importantly, the study protocol should clearly define the criteria for initiating rescue medication and ensure corresponding data collection. Criteria to initiate rescue medication should be clearly operationalised in the study protocol, so that results can be interpreted adequately.

Minor changes in background treatment may be allowed without being considered to reflect treatment failure and could thus be handled with a *treatment policy strategy* if well defined, prespecified and justified in the study protocol.

For radiographic endpoints, the relevant strategy for handling the intercurrent event "initiation of rescue medication" needs to be carefully considered and justified. Important aspects to take into account include the expected effect of the investigational product, the presumed effect of the selected rescue treatments and duration of rescue treatment. A *treatment policy strategy* may be adequate but also other approaches are possible.

In addition to handling the intercurrent events in the above-described approaches, the pattern of the occurrence of intercurrent events should be reported and compared between treatment arms. Particularly, the use of rescue medication should be considered as a secondary endpoint.

Study design

In general, a randomised, three-arm study (new treatment, active comparator, placebo), double blind, parallel group design to demonstrate the superiority of the new treatment over placebo is most appropriate for generating confirmatory evidence of efficacy in PsA.

Randomisation should be stratified by region (see Guideline on General Principles for Planning and Design of Multi-Regional Clinical Trials; ICH E17) and other important stratification factors relevant for the clinical setting (e.g., previous MTX or bDMARD treatment, extent/severity of psoriasis).

The confirmatory clinical study should usually be of one year duration to allow demonstration of efficacy (usually after shorter time period, see above) and the maintenance of the effect (usually after one year of study duration). The study may include elements of re-randomisation of subjects (see above section on study treatments).

For the demonstration of slowing or prevention of structural damage, the observation period should not be less than two years.

Statistical considerations

The statistical analysis should be aligned with the estimand of interest. Analyses estimating supplementary other estimands can also assist in the interpretation of study data and may supplement benefit-risk assessment.

Efforts should be made to collect all relevant data for the primary and important other estimands (e.g. follow-up regardless of intercurrent events) to minimise the need to rely on untestable assumptions in the analysis and interpretation of the study results. Still, handling of missing data is of particular concern, as a relevant amount of missing data (often differential across treatment arms) has to be expected based on study results from the past.

Generally, the handling of missing data should be based on clinically plausible assumptions, or when a range or assumptions is plausible, adequately conservative assumptions making it unlikely that the treatment effect is biased in favour of the new treatment or its variance underestimated.

When missing data need to be imputed following treatment discontinuation, the analysis should not (implicitly) assume that all the benefit from treatment is retained, which is not considered clinically plausible. Particularly, methods based on the missing-at-random assumption are not acceptable for estimating the treatment effect regardless of treatment discontinuation if they are (primarily) based on data collected while on treatment and if they are not accounting for the actual treatment status (particularly, the discontinuation of treatment of some subjects). Alternatively, reference-based multiple imputations (with a justified assumption on the amount of benefit retained after discontinuation of treatment, if any) could be considered.

Assumptions underlying the primary analysis should be examined through pre-specified and justified sensitivity analysis (e.g. tipping point analyses) addressing the same estimand.

While the implementation of the *composite strategy* is straightforward for responder endpoints (participants experiencing the intercurrent event being classified as non-responders), there is no canonical implementation for continuous endpoints. The interpretability and operating characteristics of a proposed implementation for continuous endpoints need to be well understood and should be sufficiently conservative.

7. Safety aspects

7.1. Specific effects

The complete immune-modulatory effects of the new medicinal product should be investigated, including immune system function and immunogenicity (for biological medicinal products), and their effects on the safety (and efficacy) profile. The impact on both affected skin and joint should be reported, including information demonstrating a lack of deleterious effects. Monitoring of structural changes to the joint is expected, with a minimal duration of two years (see also section 5.2 on study design for adequate assessment of structural changes).

Adverse Events (AEs) associated with the mode of action of the medicinal product and risks known for the specific substance class should be investigated. More detailed, AEs of particular interest are infections, including severe, opportunistic, and common infections. The association between the emergence of infections and the concomitant immune parameters such as neutrophil count or immunoglobulin level need to be analysed. Other AEs of particular interest that should be reported are malignancies, Major Adverse Cardiovascular Events (MACE) and arterial thrombotic events as well as Venous Thromboembolic Events (VTE). For each of these, an independent adjudication process should be considered.

For products with a subcutaneous and / or intravenous route of administration, injection site reactions and infusion reactions should carefully be monitored, also with respect to immunogenicity, i.e. antidrug antibodies (ADA) and neutralising antibodies (nAb). The immunogenicity testing methodology (for ADA and nAb) must be validated and clinically relevant thresholds for impact should be described. The

relationship between ADA and nAb and loss of efficacy, infusion reactions, and other adverse events needs to be evaluated.

Data on previous and concomitant (skin) treatment (e.g. psoralen plus ultraviolet-A (PUVA) radiation) should be reported as these may impact the safety profile of the new medicinal product. Furthermore, comorbidities and cardiovascular risk factors in PsA should be considered.

Because AEs may emerge even after drug discontinuation, an appropriate post-treatment follow-up period should be defined; participation in PsA registries in a post-marketing setting is recommended. It is also recommended to characterise the reversibility of AEs after withdrawal.

7.2. Long-term effects

Because PsA is a chronic condition requiring long-term treatment, controlled safety data for products with new molecular entities is expected for at least 300-600 patients treated for 6 months, and in a minimum of 100 patients for at least of 52 weeks treatment before marketing authorisation (see note for guidance on The Extent of Population Exposure to Assess Clinical Safety for Drugs (CPMP/ICH/375/95; ICH E1A), unless otherwise justified. Larger datasets may be needed for immune-modulating products, in particular those affecting multiple pathways.

For biologicals, a 52 week-period is normally required to evaluate possible induction of ADA. Although this may depend on the characteristics of the medicinal product, collection of safety data during periods longer than 52 weeks is recommended to be planned, also as post-approval studies for monitoring of rare events and events with long induction time (e.g. malignancies, MACE). In case T2T with dose tapering approaches are included in the design of the pivotal studies, larger numbers of patients may need to be studied for a prolonged period of time for adequate assessment of the long-term safety profile of the new medicinal product including the proposed posology, because these approaches may challenge the attribution of AEs to a specific dose. Dose reduction or dose spacing could also be studied post-approval.

The assessment of the causality of rare events and events with long onset is generally complicated. A larger sample size and longer monitoring may be required; this can be accomplished by follow-up studies and the use of registries in the post-marketing setting.

The inclusion of an active comparator in the clinical studies enables comparison of (long-term) safety with existing therapies for contextualisation of data and is recommended. This is considered well feasible given the expanding treatment arsenal for PsA.

Medicinal products with immune suppression as mechanism of action are often developed across various rheumatological or systemic auto-immune conditions and safety may, to some extent, be extrapolated across related conditions. This is under the premise that similarity between the conditions in terms of comorbidities, comedication, and other factors influencing the risk for adverse reactions is given and comparable posology and treatment strategies are applicable. As such, an adequate justification for extrapolation is expected, including a discussion on the similarity of background factors (e.g. concomitant treatments and comorbidities) that are important for risks associated with the medicinal product.

7.3. Safety endpoints

In general, the content of ICH E1A should be taken into consideration.

Identified AEs should be characterised in relation to the duration of treatment, the applied dose, the different age groups, and other relevant variables. All AEs occurring during the course of clinical

studies must be fully documented with separate analysis of severity (mild, moderate, severe). Further, serious adverse events, adverse events leading to drug discontinuation, and fatal outcomes, should be reported. Clinical observations should be supplemented by appropriate laboratory tests, including haematology and cell counts, renal function (serum creatinine, urine protein, estimated clearance), liver enzymes and function (including alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase (AF), bilirubin, albumin), and other laboratory endpoints relevant for the medicinal product.

Whenever the development of antibodies may be expected, the rate and therapeutic consequences of ADA should be studied. Factors that influence the appearance of nAb such as duration and dose of the treatment or the concurrent use of other medicinal products should be analysed.

Specific and long-term safety endpoints to be monitored are listed above (sections 7.1 and 7.2).

8. Studies in special populations

8.1. Studies in elderly patients

PsA (like psoriasis) is a condition that affects all age categories, but late-onset PsA has distinct clinical and genetic characteristics. Although separate studies in the elderly are not required, clinical studies in PsA should include sufficient number of patients in the age categories 65 – 74, 75 – 84, and 85 years and above. Arbitrary upper age cut-offs for inclusion should be avoided. See also Note for Guidance on Studies in Support of Special Populations: Geriatrics (ICH Topic E7).

Efficacy in elderly patients

Efficacy data should be presented for the different relevant age strata across the geriatric spectrum (i.e. 65 – 74, 75 – 84, and 85 years and above) to enable assessment on whether the effects in these groups are consistent with the effects in the non-geriatric population. Age-based subgroup analysis should be pre-specified in the statistical analysis plan and appropriate sample size should be planned.

Safety in elderly patients

The safety data should be presented for the different relevant age strata across the geriatric spectrum (i.e. 65 – 74, 75 – 84, and 85 years and above).

Especially with regard to safety, data derived from a younger population may not fully be generalisable to the geriatric population. The risks for co-morbidities such as cardiovascular disorders, malignancy, and renal impairment increases with age, and concomitant drug therapies and risk of drug interaction require special considerations. Elderly patients may also be more susceptible to infections when treated with immune-modulating drugs.

The clinical development programme, including PK studies, should provide data that allow an assessment whether special warnings and precautions or dose recommendations would be applicable in elderly patients.

8.2. Studies in paediatric patients

Reference is made to the EMA 'Guideline on clinical investigation of medical products for the treatment of juvenile idiopathic arthritis' (EMA/CHMP/239770/2014 Rev. 2; section 7) in which the requirements for demonstration of efficacy and safety in the paediatric population are established.

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Definitions

ACR: American College of Rheumatology

ADA: antidrug antibodies

AE: adverse event

AF: alkaline phosphatase

ALAT: alanine aminotransferase

AS: ankylosing spondylitis

ASAS: Assessment in SpondyloArthritis International Society

ASAT: aspartate aminotransferase

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

BASRI: Bath Ankylosing Spondylitis Radiology Index

bDMARD: biological disease-modifying antirheumatic drug

BSA: Body Surface Area

CASPAR: Classification Criteria for Psoriatic Arthritis

c-DAPSA: clinical Disease Activity index for Psoriatic Arthritis

CRP: C-reactive protein

cs-DMARD: conventional synthetic disease-modifying antirheumatic drug

CT: computed tomography

DAPSA: Disease Activity index for Psoriatic Arthritis

DMARD: disease-modifying antirheumatic drug

DSS: dactylitis severity score

ESR: erythrocyte sedimentation rate

EU: European union

FACIT-F: functional assessment of chronic illness therapy - fatigue

HAQ: health assessment questionnaire

HAQ-DI: health assessment questionnaire-disability index

HR-QOL: health-related quality of life

hs-CRP: high-sensitivity CRP

ICH: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

IL: interleukin

JAKi: Janus Kinase Inhibitor

LDI: Leeds Dactylitis Index

LEI: Leeds Enthesitis Index

MACE: Major Adverse Cardiovascular Events

MASES: Maastricht Ankylosing Spondylitis Enthesitis

MDA: Minimal Disease Activity

mHAQ: modified health assessment questionnaire

mNAPSI: modified Nail Psoriasis Severity Index

MRI: Magnetic Resonance Imaging

NAPSI: Nail Psoriasis Severity Index

nAb: neutralising antibodies

NSAIDs: Non-steroidal anti-inflammatory drugs

OMERACT: outcome measures in rheumatoid arthritis clinical trials

PGA: Physician’s global assessment

PGA-F: Global Assessment of Fingernail Psoriasis

PARS: Psoriatic Arthritis Ratingen Score

PASDAS: Psoriatic Arthritis Disease Activity Score

PsA: psoriatic arthritis

PsAID: psoriatic arthritis impact of disease

PsAMRIS: Psoriatic Arthritis Magnetic Resonance Image Scoring System

PsAQOL: Psoriatic Arthritis Quality of Life

PsARC: Psoriatic Arthritis Response Criteria

PD: pharmacodynamics

PK: Pharmacokinetic

PtGA: Patient Global Assessment

PUVA: psoralen plus ultraviolet-A

QoL: quality of life

RA: rheumatoid arthritis

RF: rheumatoid factor

SAA: serum amyloid A

SASS: Stoke Ankylosing Spondylitis Spine Score

SF-36: 36-item short form survey

SJC: Swollen Joint Count

SPARCC: Spondyloarthritis Research Consortium of Canada

T2T: treat-to-target

TJC: Tender Joint Count

TNFα: Tumor Necrosis Factor alpha

tsDMARD: targeted synthetic disease-modifying antirheumatic drug

VAS: visual analogue scales

VTE: Venous Thromboembolic Events